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# The Impact of Anxiety, Depression & Cognitive Impairment on Functioning in the Physically Ill Elderly in Egypt

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## Abstract

In the elderly, depression as well as anxiety are often under-diagnosed in medical settings or simply dismissed as inevitable consequences of aging or unavoidable complication of other illnesses or treatments. So, this study was set out to detect the common psychological problems in an Egyptian sample of the physically ill elderly. Depression, anxiety state/trait and cognitive dysfunction and their relation to various medical problems as well as their impact on the different forms of functioning were studied. One hundred elderly patients recruited from the inpatient unit as well as the outpatient clinic in the Geriatric Medicine Department, Ain Shams University Hospitals, were assessed using Instrumental Activities of Daily Living (IADL), Activities of Daily living (ADL), health promotion questionnaire, Mini Mental State Examination (MMSE), Geriatric Depression Scale (GDS, 30 items), State-Trait Anxiety Inventory (STAI), as well as assessment for the different medical conditions. Only 26% had mild cognitive impairment according to MMSE, 64% were severely depressed according to GDS & 72% were suffering from anxiety as assessed by STAI & 35% had anxiety trait by the same scale. Moreover, 47% were dependant as regards IADL and 26% as regards ADL. Neither depression nor anxiety trait were associated with any socio-demographic or clinical variables ($P>0.05$). However, it was found that functional impairment on IADL was significantly associated with depression ($X^2=4.496$, $P=0.028$), and functional impairment on ADL showed a highly significant association with depression and anxiety trait ($X^2=13.167$, $P<0.001$ for both). Regardless of their cause, depression as well as anxiety should be disentangled from any other disorder, particularly from physical disorders, so that the most appropriate treatment can be prescribed as timely intervention can reduce the incidence of undesirable consequences including suicide.

## Introduction

The developmental demands of late life are many; coping with physical illness, disability, or diminished capacity for physical activity. Also, risk for mood disturbances in late life remains high. Depression is one of the most common psychiatric disorders among the elderly. The prevalence of clinically significant depressive symptoms ranges from 8-15% among community dwelling elderly persons and is about 30% among the institutionalized elderly. Moreover, some medical disorders are associated with depression, e.g. cancer, myocardial infarction, hyperthyroidism, hypothyroidism and Parkinson diseases (Blazer, 2000).

Three factors combine to make depression in late life a primary concern in worldwide public health. First, the global population is growing older, gaining nearly 30 years of life expectancy (Lebowitz et al., 1998). Second, the appreciation of the disabling consequences of depression has been underscored by landmark report of the World Health Organization on the “global burden of disease" (Murray & Lopez, 1996). Third, the tools of contemporary neuroscience have significantly enhanced our understanding of the pathophysiologic and etiologic mechanisms of depression (Duman et al., 1997; Kumar et al., 1998; Musselman et al., 1998). Moreover, majority of people elder than the age of 65 years have at least one chronic physical disorders, so it is not surprising that comorbidity between depressive disorders and physical illnesses is substantial among elderly.

Also, problems with anxiety are common among the elderly, affecting 5-20% of the population older than 65 years at any given time. Persistent anxiety can diminish functional capacity and quality of life as well as negatively influence a number of medical disorders. On the other hand, there are many medical disorders that may cause anxiety in the elderly such as cardiac arrhythmias, delirium, dementia, depression, hyperthyroidism, hypoglycemia; some drugs may also cause anxiety as anticholinergic drugs and pseudoephedrine (Blazer & George, 1991; Limdesay, 1991; Blazer, 2000). Despite all these facts systematic studies of anxiety disorders among the physically ill elderly are rather scant.

Many reports indicate that patients with combined chronic illness and depressive and/or anxiety symptomatology have more disability than those with physical illness alone, which may influence physician visits. Studies suggest that these combined conditions are unevenly accommodated by the delivery system and non-psychiatric physicians often fail to recognize or treat these symptoms.

Also, dementia is one of the most serious disorders affecting the elderly. The prevalence of dementia increases rapidly with age and doubles every 5 years (Marcantonio, 2000). Moreover, dementia is present in a significant proportion of patients admitted to general inpatient units. Patients with dementia are admitted for different reasons than patients without dementia and appear to have longer stays, which are associated with higher costs (Lyketsos et al., 2000). Systemic metabolic illnesses and nutritional deficiencies are common among elderly patients and may be associated with dementia. These dementias can be treated by recognizing and treating the underlying conditions (Scharre and Cummings, 1998).

Although age is not a risk factor for either anxiety or depression-factors associated with aging-such as increased medical burden of independence-are substantial risk factors for development of both conditions. Moreover, there is a close association in older people with untreated mental illness and exacerbation of physical illness. So, this study was set out to detect the common psychological problems in an Egyptian sample of the physically ill elderly (Depression, Anxiety state/trait and Cognitive Dysfunction) and their relation to the various medical problems as well as their impact on the different levels of functioning.

## Methods

### Hypotheses:

I-Psychological problems in the Egyptian physically ill elderly patients (Depression, Anxiety state/trait and Cognitive Dysfunction) are positively associated with their medical conditions.

II-Functional impairment is positively associated with depression and/or anxiety in the Egyptian physically ill elderly.

**Subjects:**

The study was conducted on a convenient sample of 100 elderly recruited from both the inpatient unit as well as the outpatient clinic in the Geriatric Medicine Department, Ain Shams University Hospitals. The department is formed of 22 inpatient beds and has four outpatient clinics weekly.

The study was performed in the period from May 2005-October 2005. Elderly patients over 60 years of age were included in the study irrespective to gender, marital status, educational level, or socio-economic status. All patients included in the study, had been only included after an oral informed consent.

All the participants were patients suffering from single or multiple system(s) disease related to the various body systems.

Patients with any of the following criteria were excluded:
1- Severely ill or uncooperative patients.
2- Patients with delirium.
3- Patients with moderate to severe dementia.
4. Patients with previous history of psychiatric disorders.

**Tools:**

*Each participant was subjected to:*

***I-Health Promotion Questionnaire:***

Included questions about routine check up, routine investigations, vaccination, cancer screening, exercise and diet control.

***II-Assessment for the following medical conditions by history, examination, as well as investigations when needed:***
-Auditory Problem
-Chest diseases
-Diabetes mellitus
-Falls
-GIT diseases
-Hypertension and other heart diseases
-Liver disease
-Nervous system diseases
-Osteoarthritis
-Prostatic diseases
-Renal diseases
-Sleep disturbance
-Urinary incontinence
-Visual problem

***III-Functional assessment:***

***1- Instrumental Activities of Daily Living (IADL) (Lawton & Brody, 1969):***

These abilities are high level abilities that allow a person to function independently at home or in the community. Early functional loss often occurs in the area of transportation and housework. It includes the following:
1- Using the telephone.
2- Get to places beyond walking distance.
3- Go shopping.
4- Preparing meals.
5- Doing housework or handyman work.
6- Taking medications.
7- Handling money.

Only the highest level (i.e., needs no help or independent) of functioning receives a score of 2, while a score of 1 means that the patient needs some help (i.e., assisted), and 0 stands for the inability to do that activity at all (i.e., dependent). These scores are useful for indicating specifically how a person is performing at the present time.

***2-Activities of Daily Living (ADL) (Katz et al., 1963):***

These are the basic activities a person must posses to remain at home independently. These abilities allow a person to do basic self-care tasks, which are referred to as activities of daily living. It is divided into 6 categories:

1- Bathing.
2- Dressing.
3- Toileting.
4- Transfer.
5- Continence of bowel and bladder.
6- Eating.

If an elderly is independent in all ADL, then elderly is able to function at home without assistance. Clients are scored yes/no for independence in each of the six functions. A score of 6 indicates full function (independent), 4 indicates moderate impairment (assisted), and 2 or less indicates severe functional impairment (dependent).

### *IV-Assessment of Cognitive functions:*

This was done using Mini Mental State Examination (Folestein et al., 1975) Arabic version (El Okl, 2002). Cognitive impairment is stated when the patient's score on MMSE is equal to or less than 24.

### *V-Assessment of depression by Geriatrics Depression Scale (GDS)*

It was conducted to assess the mood state in the elderly patients. The Geriatrics Depression Scale (GDS) was designed originally by Yasavage et al. (1983). It represents a reliable and valid self-rating depression screening scale for elderly population. It was translated and validated on Egyptian population by Abdel Sameea (1997). The scale included 30 items, taking only 10-15 minutes to administer, and if the subject scored 11 or higher positive items, he/she is considered depressed. If the patient scored 11-20 he/she is considered mildly depressed, however, if the patient scored 21-30, he/she is considered to be severely depressed.

### *VI-Assessment of Anxiety by State-Trait Anxiety Inventory (STAI):*

The State-Trait Anxiety Inventory (STAI) was originally designed by Spielberger (1970). It is a definitive instrument for measuring anxiety in adults. The STAI clearly differentiates between the temporary condition of "state anxiety" and the more general and long-lasting quality of "trait anxiety". The essential qualities evaluated by the STAI are feelings of apprehension, tension, nervousness, and worry. It included two questionnaires, one for assessment of anxiety state and the other for trait assessment. It is formed of 40 items taking only 15-20 minutes to administer, provides an acceptable and valid screening test for anxiety in the elderly subjects. The Arabic version used in this study is by Abd El Khalek (1992).

## Statistics

Statistical Package for social science (SPSS) program, version 11.0.1 was used for analysis of data as follows:

1-Descriptive statistics were carried out in the form of mean, standard deviation, and range for all quantitative values.

2-Frequency and percentage was done for qualitative variables.

3- Analytic statistics in the form of chi-square and t-test.

## Results

### ***1-Socio-Demographic Data***

Our sample was formed of 100 patients, 52 (52%) males and 48 (48%) females. The mean age was 65.64 (±5.57) years. As regards their marital status, 57 (57%) were married, 40 (40%) were widowers/widows, 2 (2%) were single, and only one (1%) was divorced. Eighty-five patients (85%) were not currently working, while 15 (15%) were working. Most of the patients 62 (62%) were illiterate, 18 (18%) can only read and write, 11 (11%) had not finished primary education, 7 (7%) received from 6-12 years of education, and only 2 (2%) finished university.

It was found that 38 (38%) were living with a spouse and kids, while 27 (27%) were living with their kids only, and 13 (13%) with a spouse only. Only 22 (22%) were currently living alone.

## 2- Clinical Characteristics of the Patients

Regarding their smoking status, 53 (53%) were non-smokers, 26 (26%) quitted smoking, and 21 (21%) were currently smokers.

Regarding the psychiatric manifestations in our sample, 64 (64%) patients were severely depressed according to the Geriatric Depression Scale. They were divided into 30 males (i.e., 57.7% of males) and 34 (i.e., 70.8% of females). On the other hand, 72 (72%) were suffering from anxiety state as assessed using STAI. They were divided into 37 males (i.e., 71.2% of males) and 35 females (i.e., 72.9% of females). On the other hand, 34 (34%) had anxiety trait as assessed by STAI; they were divided into 18 males (i.e., 34.6% of males) and 16 females (i.e., 33.33% of females). Regarding the cognitive impairment in our patients, 74 (74%) showed no impairment as assessed by Mini Mental Status Examination, and only 26 (26%) had mild impairment. They were divided into 12 males (i.e., 23.1% of males) and 14 females (i.e., 29.2% of females). There were 46 (46%) suffering from insomnia. They were equally divided into 23 males (i.e., 44.2% of males) and 23 females (i.e., 47.9% of females) There was no statistically significant difference ($P>0.05$) as regards sex distribution of the different psychiatric symptomatology in our sample.

As regards functioning in our sample, none were totally independent either on ADL or IADL, while 47% of the patients were dependent as regards IADL and 26% as regards ADL.

It was found that health promotion in this sample was quite poor. None of our patients took the essential vaccinations, or followed cancer-screening program. The female patients never went for cancer screening for breast or cervix.

Neither depression nor anxiety trait was significantly associated with any of the socio-demographic variables, smoking, health promotion, or physical illnesses ($P>0.05$). However, anxiety state showed a highly significant association ($X^2=28.901$, $P=0.001$) with diabetes, cardiovascular diseases, osteoarthritis, renal disease, chest disease, as well as multiple systems affection. It is worth mentioning that none of the patients with Parkinsonism or liver disease had anxiety state, yet most of them had severe depression (75% and 66.67% respectively).

Moreover, we found that non-depressed state showed a statistically significant ($P<0.01$) association with high anxiety state and trait. It is worth mentioning that 100% of those with anxiety trait (n=34) had anxiety state ($P<0.001$). However, insomnia was not significantly associated with any of the psychological problems of the studied group ($P>0.05$).

Impaired mental state as detected by Mini Mental State Examination was significantly associated ($X^2=8.270$, $P=0.041$) with living alone, however, those with good MMSE were living with spouse and/or kids. It was not significantly associated with depression ($X^2$=0.607, P=0.292), anxiety state ($X^2$=0.422, P=0.352), or trait ($X^2$=1.868, P=0.129). It should be mentioned that those with delirium or moderate to severe dementia were excluded from the study.

On comparing patients with only one physical illness with those having multiple physical illnesses, the association between depression, anxiety state or trait, and cognitive impairment with the number of physical illnesses was not statistically significant (P>0.05).

It was found that functional impairment on IADL was significantly associated with depression ($X^2$=4.496, P=0.028), and functional impairment on ADL showed a highly significant association with depression and anxiety trait ($X^2$=13.167, P<0.001 for both). Moreover, having multiple physical illnesses showed a highly significant association with functional impairment as detected by IADL ($X^2$=60.720, P<0.001) as well as by ADL ($X^2$=50.721, P<0.001).

**Table (1) Instrumental Activities of Daily Living (IADL) & Activities of Daily Living (ADL) in the Study Group**

| | IADL | | ADL | |
|---|---|---|---|---|
| | **Number** | **Percent** | **Number** | **Percent** |
| **Dependent** | 47 | 47 | 26 | 26 |
| **Assisted** | 53 | 53 | 74 | 74 |
| **Independent** | 0 | 0 | 0 | 0 |
| **Total** | **100** | **100** | **100** | **100** |

**Table (2) Health Promotion in the Study Group**

| **Health Promotion** | **Patients** | | | | |
|---|---|---|---|---|---|
| | **No** | **%** | **Yes** | **%** | **Total** |
| **Regular check up** | 95 | 95 | 5 | 5 | **100** |
| **Routine analysis** | 90 | 90 | 10 | 10 | **100** |
| **Exercises** | 88 | 88 | 12 | 12 | **100** |
| **Diet control** | 79 | 79 | 21 | 21 | **100** |
| **Vaccinations** | 100 | 100 | 0 | 0 | **100** |
| **Cancer Screening in Females** | 48 | 100 | 0 | 0 | **48** |

**Table (3) Depression in Relation to Physical Illnesses**

| **Physical Illnesses** | **Depressed Pts** | | **Non-Depressed Pts** | | **Total** |
|---|---|---|---|---|---|
| | **Number** | **Percent** | **Number** | **Percent** | |
| **Diabetes** | 2 | 3.1 | 1 | 2.8 | **3** |
| **Hypertension** | 3 | 4.7 | 3 | 8.3 | **6** |
| **Other cardiovascular disease** | 2 | 3.1 | 1 | 2.8 | **3** |
| **Osteoarthritis** | 3 | 4.7 | 2 | 5.6 | **5** |
| **Peptic Ulcer** | 4 | 6.3 | 1 | 2.8 | **5** |
| **Renal disease** | 1 | 1.6 | 0 | 0 | **1** |
| **Chest disease** | 2 | 3.1 | 1 | 2.8 | **3** |
| **Stroke** | 1 | 1.6 | 1 | 2.8 | **2** |
| **Parkinsonism** | 3 | 4.7 | 1 | 2.8 | **4** |
| **Liver disease** | 2 | 3.1 | 1 | 2.8 | **3** |
| **Multiple systems** | 41 | 64.1 | 24 | 66.7 | **65** |

Pts=Patients $X^2$=2.473, P=0.991

**Table (4) Anxiety State in Relation to Physical Illnesses**

| Physical Illnesses | Pts with Anxiety State | | Pts without Anxiety State | | Total |
|---|---|---|---|---|---|
| | Number | Percent | Number | Percent | |
| **Diabetes** | 3 | 4.2 | 0 | 0 | 3 |
| **Hypertension** | 4 | 5.5 | 2 | 7.1 | 6 |
| **Other cardiovascular disease** | 3 | 4.2 | 0 | 0 | 3 |
| **Osteoarthritis** | 5 | 6.9 | 0 | 0 | 5 |
| **Peptic Ulcer** | 3 | 4.2 | 2 | 7.1 | 5 |
| **Renal disease** | 1 | 1.4 | 0 | 0 | 1 |
| **Chest disease** | 3 | 4.2 | 0 | 0 | 3 |
| **Stroke** | 1 | 1.4 | 1 | 3.6 | 2 |
| **Parkinsonism** | 0 | 0 | 4 | 14.3 | 4 |
| **Liver disease** | 0 | 0 | 3 | 10.7 | 3 |
| **Multiple systems** | 49 | 68 | 16 | 57.1 | 65 |

Pts=Patients $X^2=28.901$, $P=0.001$

**Table (5) Anxiety Trait in Relation to Physical Illnesses**

| Physical Illnesses | Pts with Anxiety Trait | | Pts without Anxiety Trait | | Total |
|---|---|---|---|---|---|
| | Number | Percent | Number | Percent | |
| **Diabetes** | 0 | 0 | 3 | 4.5 | **3** |
| **Hypertension** | 3 | 8.8 | 3 | 4.5 | **6** |
| **Other cardiovascular disease** | 1 | 2.9 | 2 | 3 | **3** |
| **Osteoarthritis** | 1 | 2.9 | 4 | 6.1 | **5** |
| **Peptic Ulcer** | 2 | 5.9 | 3 | 4.5 | **5** |
| **Renal disease** | 0 | 0 | 1 | 1.5 | **1** |
| **Chest disease** | 0 | 0 | 3 | 4.5 | **3** |
| **Stroke** | 2 | 5.9 | 0 | 0 | **2** |
| **Parkinsonism** | 2 | 5.9 | 2 | 3 | **4** |
| **Liver disease** | 1 | 2.9 | 2 | 3 | **3** |
| **Multiple systems** | 22 | 64.7 | 43 | 65.2 | **65** |

Pts=Patients $X^2=11.771$, $P=0.301$

**Table (6) Cognitive Impairment in Relation to Physical Illnesses**

| **Physical Illnesses** | **Pts with Cognitive Impairment** | | **Pts without Cognitive Impairment** | | **Total** |
|---|---|---|---|---|---|
| | **Number** | **Percent** | **Number** | **Percent** | |
| **Diabetes** | 1 | 3.8 | 2 | 2.7 | **3** |
| **Hypertension** | 1 | 3.8 | 5 | 6.8 | **6** |
| **Other cardiovascular disease** | 1 | 3.8 | 2 | 2.7 | **3** |
| **Osteoarthritis** | 1 | 3.8 | 4 | 5.4 | **5** |
| **Peptic Ulcer** | 0 | 0 | 5 | 6.8 | **5** |
| **Renal disease** | 0 | 0 | 1 | 1.4 | **1** |
| **Chest disease** | 0 | 0 | 3 | 4.1 | **3** |
| **Stroke** | 0 | 0 | 2 | 2.7 | **2** |
| **Parkinsonism** | 1 | 3.8 | 3 | 4.1 | **4** |
| **Liver disease** | 1 | 3.8 | 2 | 2.7 | **3** |
| **Multiple systems** | 20 | 76.9 | 45 | 60.8 | **65** |

Pts=Patients $X^2$=8.003, P=0.629

## Discussion

The most common psychiatric disorders in later life, with the exception of dementia, are depression and anxiety (Fernandez et al., 1995). Psychiatric morbidity in the elderly is a major cause of disability. Depression in older people is a significant public health problem. It is the cause of unnecessary suffering for those whose illness is unrecognized or inadequately treated, and it burdens families and institutions providing care for the elderly. Because of the stereotypic notion that older people are necessarily beset by many physical illnesses as well as social and economic problems, some clinicians, family members, and older people themselves often conclude that depression is an inevitable part of aging or as another complication of other constitutional illnesses. Moreover, the significance of illness burden attributable to depression increases with age weighing and thus will grow further by the year 2020 based upon projected demographic shifts towards an older population (Reynolds, 1999).

In our study 64 % of the patients were severely depressed according to the GDS; this is remarkably higher than studies done in other countries, which found that the prevalence of clinically significant depressive symptoms reaching from 15% to 27% in some estimates (Fitten, 1998). However, the prevalence is very similar to that found earlier by Ashour et al. (1993) who reported 65% prevalence rate of depressive symptomatology in patients attending Ain Shams University Hospital. On the contrary, it is lower as regards prevalence of depressive symptoms than the study done in 1998 at the same university hospital on physically ill elderly as well, which found that 79.2% suffer from depressive symptoms using Geriatric Depression Scale (15 items) (Omar et al., 1998). We can conclude that depressive symptoms are really higher in elderly patients in our country, which can be explained by the fact that elderly loose their function, and this is particularly true for the physically ill elderly. If we compare this with western society, we will find that elderly may start a new career at that age and they certainly continue to enjoy being productive and active. Moreover, this variation may be due to the use of different instruments and rating scales in the assessment of depression.

Furthermore, there appears to be no clear delineation between depressive symptoms and depressive disorders among very old, physically ill adults (Kennedy & Marcus, 2005). Also, Schneider et al. (2000) found that in old age there is substantial danger of confounding major depression, subclinical depression and organic mood disorders, thus leading to erroneously high prevalence rates of major depression and underestimation of organic mood disorder if depressive symptoms are recorded only by self-report scales or a symptom checklist. Moreover, evidence is mounting to support the notion that clinically significant depression is a spectrum disorder rather than a categorical disease entity, particularly in this age group.

Depression was not significantly associated with any of the socio-demographic or clinical variables ($P>0.05$). So, the practitioners need to know that advanced age, physical illness and depression need not go hand in hand. However, these findings were controversial, so Blazer (1999) agreed with our study in that the onset of depression was not related to sociodemographic factors at either sex. On the contrary, other studies found that female sex as well as low socioeconomic level are risk factors for depression in this population (Helmer et al., 2004). This might explain the high prevalence of depression in our patients, as they all came from low socioeconomic class.

Despite the fact that symptoms of anxiety are considered to be common in the elderly. These numbers were remarkably high (72%) in our study. Community studies in other countries as USA show that anxiety symptoms are present in about 20% of aged individuals (Blazer & George, 1991). Heun et al. (2000) in Germany as an example of European community, found that although 4.9% of the subjects had a diagnosis of major depression, 31.8% had either minor or recurrent depression, 6.6% had a major anxiety disorder, and 18.5% had a subthreshold anxiety disorder.

In our study, the best predictor of having anxiety state in the physically ill elderly was having anxiety trait ($P<0.001$). Also, it was found that non-depressed state was associated with statistically significant ($P<0.001$) high anxiety state and trait. So, this led us as many other clinicians to question whether anxiety disorders in the elderly are indeed distinct or simply different expressions of major depressive disorder. Also, Heun et al. (2000) in Germany did not find increased comorbidity between major and subthreshold depressive and anxiety disorders. This contradicts with what Reynolds (1999) found that in the elderly depression and anxiety are highly correlated, as depressed elderly may present with anxiety symptoms. Moreover, Lenz (2003) found that elderly patients with depression commonly suffer from concurrent symptoms of anxiety or comorbid anxiety disorders. Such comorbidity is associated with a more severe presentation of depressive illness, including greater suicidality.

Our results showed that there was no statistically significant association ($P>0.05$) between any certain medical disorder and depression despite the high frequency of depression in general in this sample of physically ill elderly. This was true when this group of physically ill elderly were compared among themselves (i.e., when those with single physical illness were compared with those with multiple illnesses). This contradicts with the general conclusions from the available literature that medical illness can be both cause and a consequence of depression (Katz, 1999). A previous Egyptian study in general medical inpatient departments had shown that depression was significantly related to heart failure, renal failure, liver failure, cerebrovascular stroke and cancer. However, it had a highly significant relation to hypertension, and an insignificant statistical relation to Parkinsonism, diabetes mellitus, peptic ulcer, chest disease, visual and hearing handicap (Omar et al., 1998).

It was found that functional impairment on IADL was significantly associated with depression ($X^2=4.496$, $P=0.028$), and functioning on ADL showed a highly significant association with depression ($X^2=13.167$, $P<0.001$). This agrees with the suggestion that adjustment disorders account for many depressive symptoms exhibited by older adults. According to this explanation, depressive symptoms frequently ensue as a reaction to a chronic or painful physical illness that decreases functional capacity, which was considered the commonest factor (Blazer, 1999). Thus, we can conclude that it is the disability rather than the type of the physical illness that is associated with depressive symptoms. On the other hand, Omar et al. (1998), has shown that there was no significant statistical relation between depression and functional impairment as measured by ADL, this draws our attention that there must be a change in the social structure of our country, which used to be mainly formed of extended families where the elderly are respected and served with dignity even if physically ill, towards a society that is formed mainly of nuclear families where physically-ill elderly lack social support and have to depend on themselves, hence they suffer according to the degree of their functional impairment.

Unfortunately, no measure of the level of disability resulting from the health event or the severity of health event is currently available. Moreover, IADL are affected to some extent in all the physically ill elderly, so it is not an accurate measure of dysfunction in this group, however, when it comes to impairment on ADL, this is perceived by the elderly as severe dysfunction as they cannot manage the simplest requirement for living unassisted at their homes.

Anxiety state showed a highly significant association ($X^2=28.901$, $P<0.001$) with physical illness in general and this anxiety was more prevalent among patients suffering from more perceived decline in their functioning (diabetes, cardiac, osteoarthritis, kidney, chest, as well as multiple systems affection). On the other hand, in France, it was found that neurological diseases, renal insufficiency, osteo-articular disease, insulin-dependent diabetes and coronary heart disease were more often considered as responsible for the concomitant major depressive episode and more often followed up in psychiatric settings than other pathologies (Consoli, 2003). Moreover, functioning on ADL showed a highly significant association with anxiety trait ($X^2=13.167$, $P<0.001$).

This agrees with what de Buers et al. (1999) found that anxiety has a clear negative impact on the functioning and well-being of older subjects. They also found that the similarity of participants with an anxiety disorder and those having merely anxiety symptoms regarding quality of life variables and health care use was quite striking.

However, neither depression nor anxiety state was significantly associated (P>0.05) with stroke in our sample, despite the seriousness of their illness, as those suffering from stroke were only two, which is small number to assess the significance of association. It is worth mentioning that all patients with stroke had anxiety trait, which might be a predisposing factor, but this needs larger sample to conclude. Also, none of the patients with Parkinsonism or liver disease had anxiety state, despite the fact that most of them had severe depression (75% and 66.67% respectively). This suggests that depression in these patients is organic rather than reactive to their symptoms. Also, this needs a larger sample to conclude.

In our study there were 46 (46%) suffering from insomnia, this was an expected finding as sleep is affected both by depression and anxiety. However, it was not significantly associated with any of the psychological problems of the studied group (P>0.05). It is worth mentioning that other causes related to the medical problems may affect the sleep patterns such as: benign prostatic hypertrophy and uncontrolled diabetes, both due to increased tendency to urinate at night either due to frequency in the former or due to polyuria in the later, as well as parasthesia which is more severe at night in diabetes. Also, sleep problems were found in heart failure patients who tend to have dyspnea at night.

One of the important findings in our study was that impaired mental state as detected by Mini Mental State Examination was significantly associated (P<0.05) with living alone, however, those with good MMSE were living with spouse and/or kids. This can be explained by the fact that having somebody living with elderly might delay cognitive impairment by providing input into memory. However, it should be noticed that those with moderate to severe dementia were excluded from our study.

Despite its prevalence and seriousness, depression and/or anxiety in late life remains under-appreciated as a source of disability and suffering for older people and their families. It is also worth mentioning that treatment of depression, regardless of the clinical context in which it occurs, can have a positive effect on the quality of life, functioning, and health. Yet, despite the fact that effective treatments are available, negative attitudes on the part of professionals and of elderly themselves about psychiatric treatment remain barriers to treatment.

Primary care providers are charged with greater responsibility for diagnosis, treatment, and long-term management in all health care, including care of older patients with mental disorders. Regardless of its cause, depression and/or anxiety requires careful evaluation by the clinician, for it must be disaggregated from other diseases, so that the most appropriate therapy can be prescribed. Effective treatment and management are available for both disorders, and timely intervention can reduce the incidence of undesirable consequences such as lowered quality of life, isolation, high mortality rate, diminished functional capacity, added medical morbidity, and suicide. Also, efforts to identify dementia early during hospitalization could improve patients' care and reduce costs. It seems advisable therefore to consult geriatric specialists in all but the most uncomplicated and treatment-responsive cases.

Our study had limitations, as the number of patients was relatively small, so when the statistics were done for each physical illness the numbers were rather small. Also, the sample of patients was not representative of the physically ill elderly in general as those presenting for the Geriatric Unit in a University Hospital are usually those with the most severe cases, also they come from low social class as compared to those presenting to hospitals from the private sector. So, future studies should include a larger sample preferably multi-center to include more patients from many other social classes. We also need to reevaluate the cut off point of the GDS (Arabic version) to our culture in the new Millennium.

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## تأثير القلق والإكتئاب وقصور الوظائف المعرفية
## على الحالة الوظيفية للمرضى المسنين

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# Diagnostic and Prognostic Values of Single Photon Emission Computed Tomography in Neuropsychiatric Manifestations of Systemic Lupus Erythematosus: An Egyptian Study

***Kamel F, AL-Gogary A, Khodeir A, Haroun El Rasheed A, Youssof N, AL-Shishtawy H***

## Abstract

Although systemic lupus erythematosus (SLE) with involvement of central nervous system (CNS), which is often called neuropsychiatric SLE (NPSLE), is one of the most important manifestations of SLE, yet there is no single test to date that serves as the gold standard for its diagnosis. So, the aim of this work was to study the diagnostic value of SPECT in CNS affection in SLE patients as well as to study its prognostic value in these patients. Also, we set out to study the role of prolactin and anti-ribosomal antibodies (anti-P) in CNS affection in SLE patients. Moreover, we aimed to detect the possible relationship between findings using SPECT and the different disease parameters. We studied 30 Egyptian SLE female patients diagnosed according to the American College of Rheumatology (ACR) criteria for the classification of SLE (1999). Ten normal healthy subjects were also included as a control group. SLE patients were categorized into 3 groups: Group I with major NPSLE (n=7); Group II with only minor NPSLE (n=3); and Group Ill without NPSLE (n=20). They had undergone physical as well as neurological history and examination; followed by assessment of disease activity using SLE Disease Activity Index (SLEDAI). Assessment for psychiatric morbidity using General Health Questionnaire (GHQ), followed by ICD-10 Symptom Checklist for those exceeding the cutoff point on the GHQ. Then they were psychometrically assessed using Beck Depression Inventory (BDI), Hamilton Anxiety Scale (HAS), and Wechsler Memory Scale (WMS). Also, they had undergone laboratory investigations including prolactin and anti-ribosomal antibodies (anti-P); EEG; CT; as well as SPECT. On the other hand, controls were subjected to GHQ to ensure that they were free from psychiatric morbidity, laboratory investigations, and SPECT. Abnormal SPECT scan was found in 83% of group I as compared to 33% of group II. However, normal SPECT scan was found in 72% of group III and in 100% of the control group. Moreover, prolactin and anti-P antibody level were the only disease parameters that showed a significant association with cerebral hypoperfusion detected on SPECT. It was also found that SPECT findings were correlated with changes that occur within the six months follow-up period in neuropsychiatric symptoms as well as with follow-up SPECT findings. So, it might be promising as a prognostic tool in NPSLE. These results confirm that SPECT is a sensitive tool both for the diagnosis as well as the prognosis of CNS involvement in SLE.

## Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune, multi-system disease with a broad spectrum of clinical manifestations. SLE with involvement of central nervous system (CNS), which is often called neuropsychiatric SLE (NPSLE), is one of the most important manifestations of SLE. The condition may be both neurological and psychiatric ***(ACR, 1999)***. The clinical manifestations of NPSLE may be obvious-for example, psychosis, stroke, and epilepsy, or there may be more subtle symptoms, such as headache and neurocognitive dysfunction ***(Denburg et al., 1994)***.

Neuropsychiatric events are seen in 14-75% of SLE patients with a wide range of clinical syndromes ***(McCune & Golbus, 1988)***, yet they are the least understood. NPSLE was shown by ***Jonsson et al. (1989)*** to be a predictor of a high frequency of flares and to be a major cause of longstanding functional impairment as well as being associated with high mortality rate. Although NPSLE is a serious manifestation of the disease, yet there is no single test to date that serves as the gold standard for the diagnosis of NPSLE.

Moreover, the diagnosis of NPSLE can be difficult as it has to be differentiated from neuropsychiatric complications that result from hypertension, drugs, infections, uremia, and metabolic changes. Thus, the occurrence of neurological and psychiatric symptoms may create a diagnostic challenge, and a determination of the origin of symptoms may be impossible when it is based solely on clinical information. The uncertainty of the origin of the symptoms is particularly troubling, because if intrinsic brain involvement is suspected, medications such as chemotherapeutic agents with severe side effects may be prescribed. Therefore, a misdiagnosis that results in over-or under-treatment is a serious risk for patients who have NPSLE.

Single photon emission computerized tomography has been used to evaluate regional cerebral blood flow and proves accurate in detecting many neurological and psychiatric diseases ***(Lewis et al., 1992)***. The advantages of SPECT are that it is non-invasive, enables anatomic imaging of lesions and most important it is a mean of functional imaging. Radiopharmaceutical uptake in the brain can be quantified and therefore function of brain can be known. Altered perfusion reflects abnormal function; therefore we can get information regarding reversibility of a lesion by objectively documenting improvement in its perfusion ***(Kovacs et al., 1995)***.

So, the aim of this work was to evaluate the diagnostic value of SPECT in CNS affection in SLE patients as well as to study it as a prognostic tool in these patients. Also, we set out to study the role of prolactin and anti-ribosomal antibodies (anti-P) in CNS affection of SLE patients. Last but not least, we aimed to detect the possible relationship between findings using SPECT and the different disease parameters.

## Methods

### Hypotheses

1-There is a positive association between cerebral hypoperfusion detected by HMPAO-SPECT and the presence of neuropsychiatric manifestations in SLE patients.

2- There is a positive association between cerebral hypoperfusion detected by HMPAO-SPECT and the different disease parameters.

Thirty consecutive SLE female patients diagnosed according to the 1999 criteria of the American College of Rheumatology (ACR) for the diagnosis of SLE were included in this study. They were selected from SLE patients who used to attend the Outpatient Clinic of the Rheumatology and Rehabilitation Department as well as from the inpatient units of the Internal Medicine Department of Ain Shams University Hospitals.

Pregnant as well as nursing females were excluded from the study. Patients with past history of epilepsy or psychiatric disorders as well as patients with apparent steroid-induced psychiatric disorder were excluded from the study. Also, we had to exclude patients with liver disease or those on contraceptive pills or taking drugs that interfere with prolactin levels as typical antipsychotics, oestrogen, and bromocriptine.

Ten normal healthy subjects were included in the study as a control group. They were selected from employees in the Department of the Rheumatology and Rehabilitation as well as patients' relatives. They were matched for age, sex, and socioeconomic status with SLE patients.

An informed oral consent was taken from all participants in the study.

Every patient was subjected to the following:

- Full medical history taking.

- A thorough clinical examination.

- Neurological examination.

- General Health Questionnaire (GHQ) to identify psychiatric morbidity. It was initially developed as a first stage screening instrument for psychiatric illness in order to identify potential "cases" which could then be verified and the nature of which could be determined by using a second stage instrument. Used in this way, the GHQ was found to be an effective measure of case identification when validated in a number of studies based on general practice or clinical attenders. The short 28-item version was the one used in this study. The cutoff score used was 4/5 (a score within the range of 0-4 representing absence of psychopathology) ***(Goldberg & Williams, 1983)***. The Arabic version used in this study is by ***Okasha et al. (1988)***.

- Patients exceeding the cutoff point on the GHQ were diagnosed using the ICD-10 Symptom Checklist ***(Janca et al., 1994)***. It consists of a symptom list that may help the user to check the presenting symptoms plus considering the possible psychiatric syndromes according to the ICD-10 Research Diagnostic Criteria.

**Neuropsychiatric symptoms:**

The diagnosis of NPSLE was made on the basis of clinical as well as ICD-10 Symptom Checklist after the exclusion of other causes of neuropsychiatric symptoms, as required by American College of Rheumatology ***(ACR, 1999)***.

Classification of NPSLE was adapted from ***ACR (1999)*** as well as ***How et al. (1985)***, in which major or minor neurological and psychiatric symptoms were operationally defined as follows: 1) major neurological symptoms which include seizures, focal motor/sensory deficits, or altered consciousness; 2) minor neurological symptoms which include paraesthesia with no objective findings, clumsiness with no objective findings, headache, or pseudo-papilloedema; 3) major psychiatric symptoms which include psychotic or mood disorders; or 4) minor psychiatric symptoms include which include cognitive dysfunction, adjustment disorders, anxiety disorders, dissociative disorder, or emotionally labile disorder.

It is worth mentioning that ***ACR (1999)*** included the neuropsychological abnormalities with the neuropsychiatric abnormalities of SLE. Therefore, these symptoms have become one more sign of the involvement of the central nervous system.

**Psychometric testing:**

1-Wechsler Memory Scale ***(Wechsler, 1945)***. It provides a broad assessment of predominantly short-term memory and learning. It takes 45 minutes to administer and is formed of the following subtests: information, orientation, mental control, logical memory, visual reproduction, digit span, and paired associate learning. Normal value for individuals below 35 years is 68.1 ± 6.5 and for individuals above 35 years is 58.8 ± 7.1. The criteria for the presence of cognitive impairment were based on impairment in the global memory or on impairment in at least three of the seven independent areas of cognitive function ***(Hanly et al., 1993)***. The Arabic version used in this study is by ***Ghanem (1981)***.

2-Beck Depression Inventory ***(Beck & Steer, 1993)***. It is a self-applied questionnaire consisting of 21 items that include cognitive components of depression to a greater degree than the behavioral and somatic ones. It is not a diagnostic instrument, but instead it provides a measure of the depth of the depression in patients with any diagnosis. The scores on this instrument can be classified into: (0-9) no depression, (10-16) mild depression, (17-29) moderate depression and ($\geq$30) severe depression. The Arabic version used in this study was by ***Abdel Khalek (1996)***.

3-Hamilton Anxiety Scale ***(Hamilton, 1976)***. It is the most widely utilized assessment scale for anxiety symptoms, and was originally intended to be used to evaluate individuals who are already diagnosed with anxiety disorders. The scores on this instrument can be classified into: (<17) mild anxiety, (18-24) mild to moderate anxiety and (25-30) moderate to severe anxiety. The Arabic version used in this study is by ***Fatim (1992)***.

**SLE disease activity index**

SLE disease activity index (SLEDAI) according to ***Bombardier et al. (1992)*** was performed. It consists of 24 descriptors with pre-assigned severity weights. The total SLEDAI score can range from 0 (no activity) to 105 (maximum activity). Patients with a score > 10 were considered active. The SLEDAI has been shown to be sensitive to changes in lupus activity measured by the treating physician.

**Neurophysiology:**

EEG.

**Laboratory investigations:**

- CBC.
- ESR.
- Serum creatinine.
- AST and ALT.
- Complete urine analysis.
- ANA.
- Detection of anti-ds-DNA autoantibody, which was performed using Autostat II autoantibody test kit supplied by Congent Diagnostic Ltd.
- Antiribosomal antibodies (anti-P) by ELISA using a kit that was supplied from ORGENTEC diagnostic Gmbh Kupferbergterrasse 17-19 D-55116 Mainz Germany. Values ≥ 3.8 IU were considered to be seropositive.
- Serum prolactin hormone level by ELISA using a kit that was supplied from EUROGENETICS. N.V. Transportstraat 4-3980 tessenderlo Belgium. Prolactin levels were determined during the first part of the menstrual cycle (between the 5th and the 8th day) (hyperprolactinemia was considered $\geq$19.1 ng/ml).

**Radiological investigations:**

- Plain-x ray chest.

- Computerized axial tomography scan of the brain was done for the ten cases with clinical symptoms of CNS affection (NPSLE).

- Brain SPECT.

**Brain SPECT Technique:**

Twenty-seven patients and 10 controls were subjected to steady state measurement of cerebral blood flow. Imaging commenced 20 minutes after IV injection of 13 mCi (480 MBq) Tc-99m hexamethylene-propylene amine oxime (HMPAO). The imaging device was a single head rectangular sophy XRT gamma camera mounted to parallel hole high resolution collimator and connected to one-line computer system.

The camera head was allowed to rotate 360 around the patient's head with the cantho-metal line perpendicular to the camera surface at the anterior start point. Image acquisition was through "the step and shoot methods" acquiring 64 frames through the entire 360 circular rotation. Images were reconstructed using appropriate filter (Butter worth) in the transverse, sagittal and coronal planes.

***Reading of SPECT:*** Method applied was visual analysis, all rCBF studies of patients and control were examined blind to the diagnosis.

***Normal tracer uptake:***

Typically there is symmetric distribution of tracer uptake in both hemispheres. The basal ganglia, occipital cortex and cerebellum will appear darker (white color) than the other regions (yellow color).

***Absent tracer uptake:***

It has the appearance of a bite or wedge taken out of the brain.

***Reduced but not absent tracer uptake:***

It appears thin or "less intense" in comparison to equivalent regions seen in normal studies. It varies from mild (orange color) to severe (green color).

***Increased tracer uptake:***

It appears to have "greater intensity" than the equivalent region seen in normal studies.

The definition of SPECT abnormalities was derived from criteria formulated by ***Lin et al. (1997)*** as follows: a single lesion or multiple small lesions confined to two lobes or less was considered to be a focal pattern, whereas the presence of lesions involving three or more lobes was regarded as a diffuse pattern.

SPECT was done for 27 patients at the beginning of the study as one patient with NPSLE died before she undergoes SPECT scanning and two patients without NPSLE refused to undergo SPECT scanning. SPECT was repeated 6 months later for 24 patients who were still alive and consenting. So, this study is considered as a longitudinal one.

So, patients had undergone physical as well as neurological history and examination; followed by assessment of disease activity using SLEDAI. Then patients were screened for psychiatric morbidity using GHQ followed by ICD-10 Symptom Checklist for those exceeding the cutoff of the GHQ. Also, they were psychometrically assessed using Wechsler Memory Scale, Beck Depression Inventory, and Hamilton Anxiety Scale. Also, they had undergone laboratory investigations; EEG; CT; as well as SPECT. All patients who were still alive and consenting were clinically as well as psychiatrically re-assessed, including repeating the psychometric testes, six months later. They had undergone a second SPECT scan after these six months as well.

On the other hand, controls were subjected to GHQ to ensure that they were free from psychiatric morbidity, laboratory investigations, and SPECT.

### Statistical Methods

The results were analyzed using the Statistical Package for the Social Science (SPSS) version 11.2.

The following statistical methods have been used in this work:

- Student test: "t-value" for comparison between means of the independent groups of patients.

- Probability of error: "P-value" used to indicate the level of significance.

- Chi-Square test: "$X^2$" which is used for comparison between two or more observed frequency distributions.

### Results

This study was carried out on 30 SLE female patients and 10 healthy matched controls. The age of patients ranged from 14-44 years (mean ± SD 25.5±8.7 years). The age of the controls ranged from 17-40 years (mean ± SD 24.3±5.7 years). Mean disease duration was 8 (±5.6 years).

### CNS affection in the patients' group:

Major CNS affection was present in 7 (23.3%) patients; 3 (10%) of them presented with seizures and cerebrovascular accident. This was associated with organic mood (affective) disorder, organic depressive disorder (moderate depression) in 2 of them (66.67%) and organic mood (affective) disorder, organic depressive disorder (severe depression) in the third. Two (6.7%) with cerebrovascular accident associated with organic mood (affective) disorder, organic depressive disorder (severe depression) and 2 (6.7%) with organic delusional (schizophrenia-like) disorder. It is worth mentioning that three patients developed coma and died, and all of them had major psychiatric manifestations as follows: 1) a patient presenting with cerebrovascular accident, seizures as well as organic mood (affective) disorder, organic depressive disorder (severe depression); 2) another patient with cerebrovascular accident as well as organic mood (affective) disorder, organic depressive disorder (severe depression); and 3) a patient with organic delusional (schizophrenia-like) disorder. On the other hand, one of the patients started by coma and recovered and she had cerebrovascular accident, seizures as well as organic mood (affective) disorder, organic depressive disorder (moderate depression).

Only minor CNS affection was present in 3 (10%) patients: two of them (6.7%) had migraine as well as cognitive impairment and one (3.33%) had only organic anxiety disorder (moderate to severe). However, it is worth mentioning that all patients with major NPSLE had minor symptoms as well.

It is also worth mentioning that all patients with NPSLE in this study, whether minor or major, had both neurological as well as psychiatric disorders, except for the two patients who had organic delusional (schizophrenia-like) disorder.

**Cognitive functions assessment in patients' group:**

Impairment of cognitive function was present in 9 (30%) patients, 7 of them had major CNS affection and two had only minor NPSLE.

**Electro - encephalography (EEG):**

EEG was done to all patients. It was found to be abnormal in 3 cases (10%); two of them with and one without clinical CNS affection.

**Serum prolactin hormone level:**

It was found that 9 (30%) patients had hyperprolactinemia (≥19.1 ng/ml). Moreover, there was a highly significant association ($P<0.001$) between hyperprolactinemia and CNS manifestations of SLE.

**Anti-ribosomal antibodies (anti-P):**

It was found that 26 patients (86.7%) were seropositive (i.e., ≥ 3.8 IU). Although 100% of patients with CNS affection had anti-P antibodies, yet this proportion was not significantly different ($P>0.05$) in those with and without CNS affection.

**Computerized tomography (CT) scans:**

CT scan was done to all patients with CNS affection (n = 10 patients). It was found to be abnormal in only 2 patients with major CNS affection.

**SPECT scan findings:**

SPECT scan was performed on 27 patients and 10 controls: Six patients with major NPSLE; 3 patients with only minor NPSLE; and 18 patients without NPSLE. One patient with major NPSLE died before SPECT scan and two patients without NPSLE refused to undergo SPECT scan. All controls showed normal SPECT scan findings (100%) and 16 SLE patients (59.3%) showed normal findings of SPECT scan. Eleven patients (40.7%) showed abnormal SPECT scan; 3 of them (11.1%) showed focal uptake defect and the other 8 patients (29.6%) showed diffuse uptake defects.

**** Patients with major NPSLE (n =6)***

Five of them had abnormal SPECT scan. Using the sensitivity test for SPECT in detecting rCBF abnormalities, it was found to be about 83% in patients with major NPSLE affection.

**** Patients with only minor NPSLE (n =3)***

SPECT scan was abnormal in 1 out of 3 (33.3%) patients with only minor NPSLE.

**** Patients without NPSLE (n =18)***

Thirteen of them had normal SPECT scan. Thus SPECT had a specificity of about 72%.

**Anatomic location of perfusion defects:**

Our results showed that hypoperfusion commonly affected the frontal lobes (10 out of 11, 91%), followed by the parietal lobes (7 out of 11, 64%) and the temporal lobes (6 out of 11, 55%), while the occipital lobes (3 out of 11, 27%) and cerebellum (2 out of 11, 18%) were the least common areas of hypoperfusion.

**Association of SPECT scans with CT results:**

**** Patients with major NPSLE (n = 6)***

CT scan showed abnormalities in only one patient in the form of infarction but it was normal in the other five. SPECT scan was found to be abnormal in the patient with abnormal CT scan findings and in 4 out of 5 patients with normal CT scan. SPECT had

100% sensitivity in detecting CT abnormalities in patients with major NPSLE and 83% sensitivity in detecting major NPSLE.

*** Patients with only minor NPSLE (n =3)***

CT scan was normal in all of them. SPECT scan was abnormal in 1 out of 3 (33.3%) patients with only minor NPSLE.

**Association of SPECT scans with EEG results:**

*** Patients with major NPSLE (n =6)***

EEG showed abnormalities in 2 patients suffering from cerebrovascular accident and seizures; however, it was normal in the other 4 patients. SPECT scan was abnormal in only one out of the two patients with abnormal EEG and abnormal in all patients with normal EEG. SPECT appears to be less sensitive than EEG in detecting seizures as a manifestation of NPSLE.

*** Patients with only minor NPSLE (n =3)***

EEG was normal in all of them. SPECT was abnormal in one out of 3 patients.

*** Patients without NPSLE (n =18)***

EEG was normal in 17 patients and abnormal in only one patient. SPECT scan was abnormal in that patient with abnormal EEG and in 4 out of 17 with normal EEG.

**Association of SPECT findings with clinical manifestations:**

There was no correlation between SPECT and clinical manifestations, including SLEDAI, other than CNS involvement.

**Association of SPECT findings with laboratory parameters:**

There was significant correlation of SPECT findings with anti-P-antibodies level ($P<0.05$) and serum prolactin hormone level ($P<0.05$), but there was no correlation with the results of other laboratory investigations ($P>0.05$).

**Follow-up SPECT after 6 months:**

SPECT analysis was repeated to twenty-four patients, as two patients with major NPSLE and one patient without NPSLE died before the second SPECT scan.

*** Patients with major NPSLE (n =6)***

Same findings was found in three out of the four (75%) with major NPSLE and improvement in only one out of four (25%). It is worth mentioning that three of these patients died, one before the first SPECT and two before the second SPECT (i.e., 42.86% mortality in patients with major NPSLE).

*** Patients with only minor NPSLE (n =3)***

Worsening in 2 out of the 3 (66.56%) patients with minor NPSLE.

*** Patients without NPSLE (n =18)***

Same findings were found in all patients without NPSLE. Improvement occurred in 1 of the 2 patients (50%) with long disease duration who received cyclophosphamide during the 6 months period between the two SPECT scans.

**Mortality rate in this sample:**

Four patients were dead by the end of the study, i.e., 13.33% mortality rate. So, three patients with major NPSLE (i.e., 42.86%) as compared to one patient without NPSLE (i.e., 5%) and none of the patients with minor NPSLE were dead by the end of the study. The difference was statistically significant ($P<0.05$) among the three groups.

**Table (1):Central Nervous System Affection in SLE Patients**

| Patient No. | Major Neuropsychiatric | | Minor Neuropsychiatric | | NOTES |
|---|---|---|---|---|---|
| | Major Neurological | Major Psychiatric | Minor Neurological | Minor Psychiatric | |
| 1 | Yes | Yes | | Yes | Cerebrovascular accident, seizures, and organic mood (affective) disorder, organic depressive disorder (moderate depression) as well as cognitive impairment |
| 2 | Yes | Yes | | Yes | Cerebrovascular accident and organic mood (affective) disorder, organic depressive disorder (severe depression) as well as cognitive impairment |
| 3 | Yes | Yes | | Yes | Cerebrovascular accident, seizures, and organic mood (affective) disorder, organic depressive disorder (moderate depression) as well as cognitive impairment. Patient started by coma and recovered |
| 4 | Yes | Yes | | Yes | Cerebrovascular accident, seizures, and organic mood (affective) disorder, organic depressive disorder (severe depression) as well as cognitive impairment. Patient developed coma and died before the first SPECT scanning |
| 5 | | Yes | | Yes | Organic delusional (schizophrenia-like) disorder as well as cognitive impairment. |
| 6 | Yes | Yes | | Yes | Cerebrovascular accident and organic mood (affective) disorder, organic depressive disorder (severe depression) as well as cognitive impairment. Patient developed coma and died before the second SPECT scanning |
| 7 | | Yes | | Yes | Organic delusional (schizophrenia-like) disorder as well as cognitive impairment. Patient developed coma and died before the second SPECT scanning |
| 8 | | | | Yes | Organic anxiety disorder (moderate to severe) |
| 9 | | | Yes | Yes | Migraine and cognitive impairment |
| 10 | | | Yes | Yes | Migraine and cognitive impairment |
| Total | 5 | 7 | 2 | 10 | |

**Table (2): Comparison between SLE Patients and the Control Group Regarding Laboratory Findings**

| LABORATORY FINDINDS | SLE Mean±SD | Control Mean±SD | T-Test | P |
|---|---|---|---|---|
| Hb (gm%) | 9.5 ± 2.3 | 14.1 ± 1.1 | -8.64 | < 0.05* |
| RBCs (106/UL) | 3.5 ± 0.8 | 4.7 ± 0.5 | -4.57 | > 0.05 |
| WBCs (103/UL) | 5.98 ± 3.3 | 6.64 ± 1.1 | -0.95 | < 0.05* |
| Platelets (103/UL) | 240.1 ± 79.6 | 252.9 ± 77.9 | -0.44 | > 0.05 |
| ESR (mm/hr) | 61.0 ± 34.9 | 9.2 ± 4.5 | 7.94 | < 0.001** |
| S. Creatinine (mg/dl) | 1.01 ± 5.3 | 0.59 ± 0.14 | 2.45 | > 0.05 |
| ALT (U/L) | 20.2 ± 6.8 | 17.4 ± 2.3 | 3.32 | > 0.05 |
| AST (U/L) | 19.3 ± 4.9 | 16.0 ± 2.0 | 2.03 | > 0.05 |

* = significant **= highly significant

**Table (3): Association of SPECT Findings with the Different Disease Manifestations**

| Disease Features | No. of Patients | Spect +Ve (N=11) | Spect –Ve (N=16) | P (Fisher's Exact Test) |
|---|---|---|---|---|
| CNS<br>-major | 7 | 5 | 1 | < 0.05* |
| -only minor | 3 | 1 | 2 | |
| -No CNS | 18 | 5 | 13 | |
| Arthritis | 24 | 10 | 14 | > 0.05 |
| No arthritis | 3 | 1 | 2 | |
| Renal disorder | 5 | 3 | 2 | > 0.05 |
| No renal disorder | 22 | 8 | 14 | |
| Chest disorder | 9 | 5 | 4 | > 0.05 |
| No chest disorder | 18 | 6 | 12 | |
| Cardiac disorder | 1 | 1 | 0 | > 0.05 |
| No cardiac disorder | 26 | 10 | 16 | |
| Hematological disorder | 10 | 6 | 4 | > 0.05 |
| No hematological disorder | 17 | 5 | 12 | |

* = significant

NB: one of the patients with major NPSLE died before doing the first SPECT scanning

**Table (4): Association of SPECT Findings with the Different Disease Parameters**

| Disease Parameter | SPECT +VE (N=11) Mean ± SD | SPECT –VE (N=16) Mean ± SD | T-Test | P |
|---|---|---|---|---|
| **ESR** | 65.4 ± 33.2 | 58.8 ± 37.2 | - 0.47 | > 0.05 |
| **Hb%** | 9.4 ±1.8 | 9.8 ± 2.6 | 0.49 | > 0.05 |
| **RBCs** | 3.4 ± 0.6 | 3.6 ± 0.9 | 0.53 | > 0.05 |
| **WBCs** | 5.7 ± 3.5 | 6.4 ± 3.3 | 0.57 | > 0.05 |
| **Platelets** | 260.9 ± 54.5 | 241.9 ± 89.1 | - 0.63 | > 0.05 |
| **S. Creatinine** | 0.9 ± 0.2 | 0.9 ± 0.2 | -0.70 | > 0.05 |
| **ALT** | 19.7± 6.3 | 21.7 ± 7.2 | 0.73 | > 0.05 |
| **AST** | 18.5 ± 3.8 | 19.1 ± 5 | 0.34 | > 0.05 |
| **Prolactin** | 13.8 ± 7.4 | 10.7 ± 5.1 | -1.21 | < 0.05* |
| **Anti-P** | 6.8 ± 3.2 | 4.5 ± 1.6 | -2.18 | < 0.05* |
| **Activity score** | 12.6 ± 7.5 | 9.3 ± 4.8 | -1.40 | > 0.05 |

* = significant

**Table (5): SPECT, CT scan and EEG results in 30 SLE patients according to Neuropsychiatric Manifestations**

| PATIENT GROUP | PT NO | SPECT | CT SCAN | EEG |
|---|---|---|---|---|
| *Major NPSLE* | 1 | Diffuse uptake defects | Normal | Background activity |
| | 2 | Diffuse uptake defects | Normal | Normal |
| | 3 | Normal | Normal | Epileptogenic focus |
| | 4 | Not done | Right and left parietal infarctions | Normal |
| | 5 | Focal left frontal region defect | Normal | Normal |
| | 6 | Diffuse uptake defects | Right parietal infarction | Normal |
| | 7 | Diffuse uptake defects | Normal | Normal |
| *Only minor NPSLE* | 8 | Normal | Normal | Normal |
| | 9 | Diffuse uptake defects | Normal | Normal |
| | 10 | Normal | Normal | Normal |
| *No NPSLE (Long disease duration, i.e., > 5 years)* | 11 | Normal | | Normal |
| | 12 | Diffuse uptake defects | | Normal |
| *No NPSLE* | 13 | Diffuse uptake defects | | Normal |
| | 14 | Normal | | Normal |
| | 15 | Normal | | Normal |
| | 16 | Normal | | Normal |
| | 17 | Diffuse uptake defects | | Epileptogenic focus |
| | 18 | Focal right parietal region defect | | Normal |
| | 19 | Focal left frontal region defect | | Normal |
| | 20 | Normal | | Normal |
| | 21 | Normal | | Normal |
| | 22 | Not done | | Normal |
| | 23 | Normal | | Normal |
| | 24 | Normal | | Normal |
| | 25 | Normal | | Normal |
| | 26 | Normal | | Normal |
| | 27 | Not done | | Normal |
| | 28 | Normal | | Normal |
| | 29 | Normal | | Normal |
| | 30 | Normal | | Normal |

PT NO= patient number

**Table (6): SPECT Scan Findings Six Months after the Initial SPECT**

| | PATIENT NO. | 1ST SPECT | 2ND SPECT | NOTES |
|---|---|---|---|---|
| ***Major NPSLE*** | 1 | Diffuse uptake defects | Same findings | Both uptake defects noted on SPECT and neuropsychiatric symptoms noted clinically unchanged despite intensification of immunosuppressive therapy. |
| | 2 | Diffuse uptake defects | Same findings | |
| | 3 | Normal | Normal | Patient symptoms controlled. |
| | 5 | Focal left frontal region defect | Improvement (normal) | Improvement of neuropsychiatric symptoms after the patient received high dose of steroids. |
| ***Only minor NPSLE*** | 8 | Normal | Worsened, it showed small perfusion defect in left frontal cortex | Persistence of neuropsychiatric symptoms, patient received steroids. |
| | 9 | Diffuse uptake defects | Same findings | Both uptake defects and neuropsychiatric symptoms were unchanged. |
| | 10 | Normal | Worsened, it showed diffuse uptake defects | Persistence of neuropsychiatric symptoms, patient received steroids. |
| ***No NPSLE (Long disease duration, i.e., > 5 years)*** | 11 | Normal | Normal | Neither developed NPSLE nor changes in their conditions. |
| | 12 | Diffuse uptake defects | Improvement in perfusion right frontal, left frontal and left parietal | Patient received cyclophosphamide during the six months period between the two SPECT scanning events. |
| ***No NPSLE*** | 13, 17 | Diffuse uptake defects | Same findings | Neither developed NPSLE nor changes in their conditions. |
| | 14,16 | Normal | Normal | |
| | 18 | Focal right parietal region defect | Same findings | |
| | 19 | Focal left frontal region | Same finding | |
| | 20 – 30 (except for the 22nd and 27th patients) | Normal | Normal | |

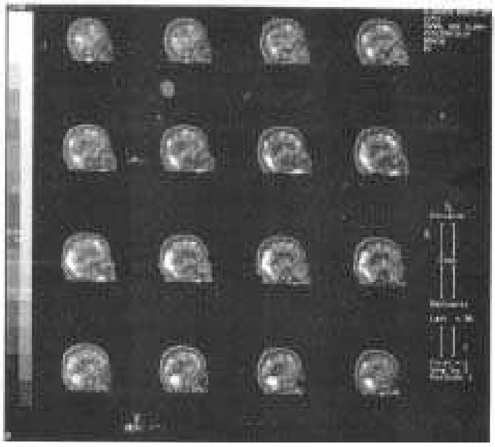

**Plate (1):** Sagittal view of the brain, normal cerebral SPECT scan.

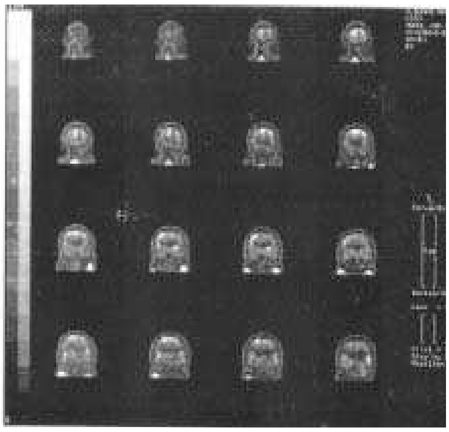

**Plate (2):** Coronal section through the cerebrum, normal cerebral SPECT scan.

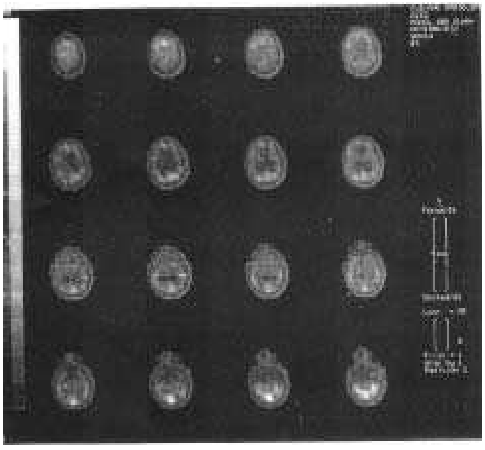

**Plate (3):** Transaxial view of the brain, normal cerebral SPECT scan

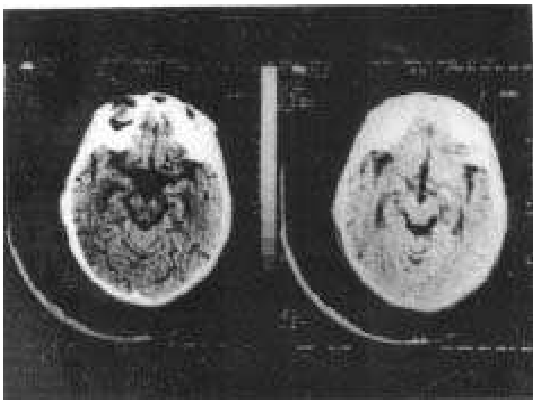

**Plate (4):** Patient no. (5): Normal CT scan.

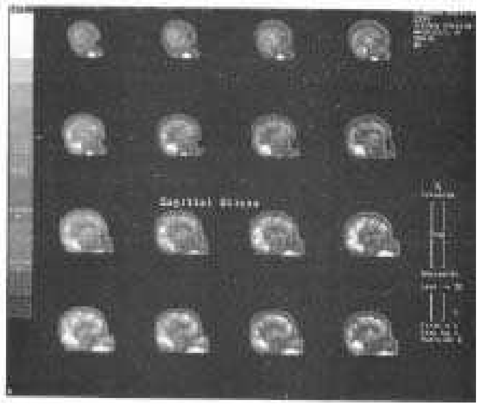

**Plate (5):** Patient no. (5): SPECT scanning showed small perfusion defect at left frontal cortex (sagittal view).

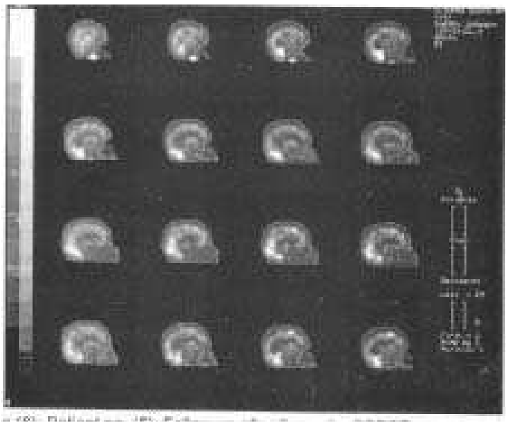

**Plate (6):** Patient no. (5): Follow up after 6 months SPECT scanning showed normal findings (Sagittal view).

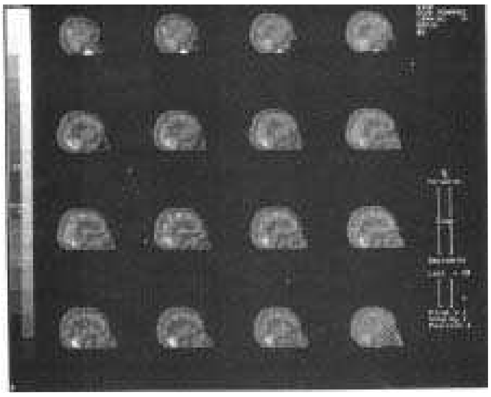

**Plate (7):** Patient no. (10): SPECT scanning showed normal findings (sagittal view).

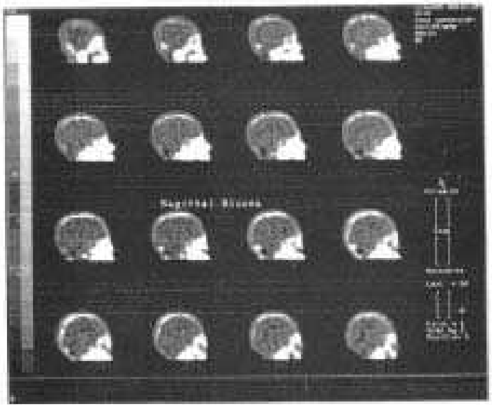

**Plate (8):** Patient no. (10): Follow up after 6 months SPECT scanning showed global hypo perfusion of cerebral cortex and cerebellum. No focal perfusion defect (sagittal view).

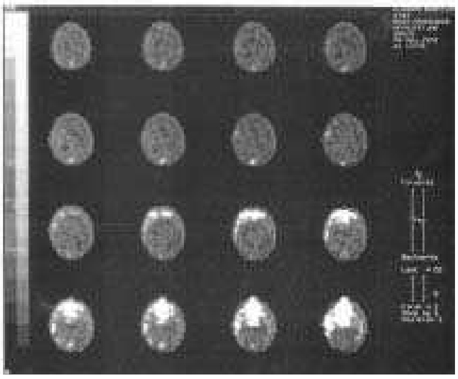

**Plate (9):** Patient no. (12): SPECT scanning showed perfusion defects in both frontal, left parietal and left occipital cortex, hypo perfusion of cerebellum and deep sub cortical structures (transaxial view).

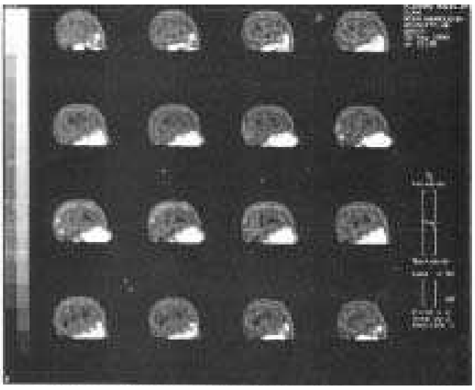

**Plate (10):** Patient no. (12): SPECT scanning showed perfusion defects in both frontal, left parietal and left occipital cortex, hypo perfusion of cerebellum and deep subcortical structures (sagittal view).

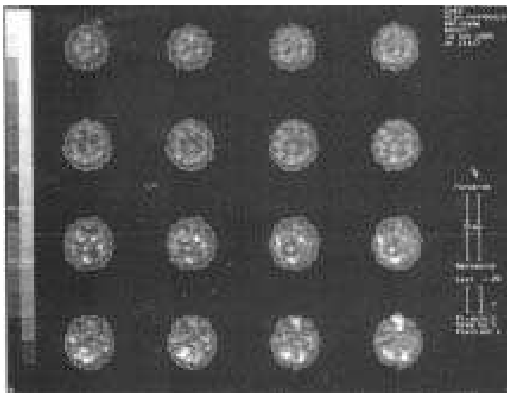

**Plate (11):** Patient no. (12): Follow up after 6 months, SPECT scan showed perfusion defects in right frontal and left occipital cortex. Rest of the brain fairly perfused (transaxial view).

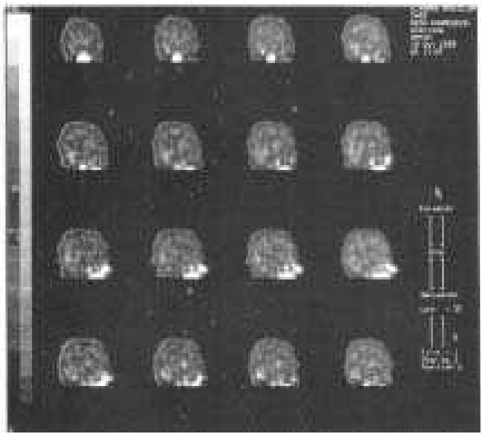

**Plate (12):** Patient no. (12): Follow up after 6 months, SPECT scan showed perfusion defects in right frontal and left occipital cortex. Rest of the brain fairly perfused (sagittal view).

## Discussion

Although involvement of the brain is one of the most important complications of systemic lupus erythematosus (SLE), yet its pathophysiology remains obscure and our understanding of NPSLE is still far from clear. First, it is difficult to distinguish between events resulting from the direct effect of active SLE on the CNS and events attributed to SLE-induced dysfunction of other organs or to side-effects of drug therapy ***(Bresnihan, 1982)***. Second, specific diagnostic methods have not been established ***(Oku et al., 2003)***.

We studied 30 Egyptian SLE female patients and 10 controls. Central nervous system affection was present in 10 (33.3%) of our patients. Our results are similar to an Egyptian study done earlier by ***Aref et al., 1992*** who reported CNS manifestations to be 33%. Also, ***Jonsen et al. (2002)*** found that NPSLE occurs in 38% of SLE patients in a Swedish sample. Other studies reported higher percentage of CNS affection in patients with SLE. ***Gibson & Myers (1976); Feinglass et al. (1976) and Grigor et al. (1978)***, suggested that CNS involvement occurs in up to 50% of SLE patients. Also, ***Bluestein (1987); McCune & Globus (1988)*** reported CNS involvement to be 75% and 66% respectively. The highest reported rate of NPSLE was by ***Ainiala et al. (2001)*** in a Finnish population, who found that 91% SLE patients had at least one NP syndrome. However, when minor manifestations were excluded, the prevalence of NPSLE dropped to 46%.

On the other hand, another study reported CNS involvement to occur in only 12%, which was lower than our study ***(Abdel-Galil et al., 1996)***. The difference in the results may be due to marked variation in the presentation, the severity and the often-transient nature of CNS affection in SLE ***(Teh et al., 1993)***. Also, the differences in methods and criteria used to define CNS affection are likely to be a major contributor to the controversial results reported ***(Bruyne,* 1995)**.

One aim of our study was to detect the diagnostic value of SPECT in CNS affection in SLE patients. Also, we compared SPECT findings with findings from clinical, neuropsychiatric, neuropsychological, laboratory, electroencephalographic (EEG) and CT scan evaluation and we studied the value of SPECT as a prognostic tool in these patients. We used SPECT scan in this situation for two reasons: the first reason is that the most consistent cerebral pathologic finding at autopsy of SLE patients has been vasculopathy ***(Johnson & Richardson, 1968)***. Because vasculitic processes are the mechanisms of cerebral symptoms in SLE, determination of rCBF as an indicator of early CNS involvement seems promising. SPECT scanning provides information on regional brain perfusion, which is closely linked to cerebral metabolism ***(Stefan et al., 1990)***. The second reason for using SPECT scan is that the diagnosis of CNS involvement is hampered by relative insensitivity of conventional imaging techniques applied in the past. MRI has been used in the diagnosis of cerebral lupus ***(Jacobs et al., 1988)***. Although it seems more sensitive than CT scan findings, both MRI and CT scan mainly correspond to structural and not functional abnormalities ***(Nossent et al., 1991)***. So, CT or MRI can reveal morphologic alteration in a substantial proportion of patients with overt neurological symptoms but it would be desirable to identify changes before structural damage occur. Functional neuroimaging by SPECT should be able to demonstrate brain perfusion abnormalities early ***(Rubbert et al.,* 1993)**. Also, in psychiatric disease, no MRI or CT defect was consistently demonstrated ***(Vermess et al.,* 1983)**.

SLE patients were categorized into 3 groups; group I with major neuropsychiatric disorders (n=7), group II with minor neuropsychiatric symptoms (n=3) and group III without neuropsychiatric symptoms (n=20). It is also worth mentioning that all patients with NPSLE in this study, whether major or minor, had both neurological as well as psychiatric disorders except for the two patients who had organic delusional (schizophrenia-like) disorder and one of them developed coma and died. Thus, an organic cause for the psychiatric disorders can be suggested and this explains the abnormal SPECT findings in these cases.

Our results revealed that 5 out of 6 patients (83%) with major NPSLE showed abnormal SPECT scan, with predominately diffuse uptake defects (in four patients out of the five, i.e., 80%). Other studies has shown SPECT to be highly sensitive, detecting abnormalities in up to 100%, 93%, and 90% of patients with clinical neuropsychiatric involvement ***(Kao et al., 1999a; Kikukawa et al, 2000; Kovacs et al., 1995*** respectively). However, SPECT has low specificity and comparable abnormalities have been described in patients with acute stroke, transient ischemic attacks, epilepsy and other neurological conditions ***(Rubbert et al., 1993)***. Thus, SPECT scanning may be used mainly to support a clinical diagnosis of neuropsychiatric involvement.

As regards SPECT as a prognostic tool for NPSLE, it was found that all patients with major NPSLE who had diffuse defects either remained unchanged or became worse clinically as well as on follow-up SPECT (two out of four, i.e., 50% died on follow-up), despite the treatment with steroids and/or immunosuppressive agents. This was in contrast to the patient with a focal defect who showed clinical improvement over time associated with improvement on her rCBF as shown on her second SPECT scanning.

Interestingly (33%) of patients with only minor NPSLE showed abnormal SPECT scan. This result is in agreement with ***kao et al. (1999a)*** who found that 33% of patients with minor manifestations of NPSLE had hypoperfusion. Moreover, in our study, all of them (100%) showed abnormal SPECT scan on follow up. This means that rCBF abnormalities are present in a substantial proportion of SLE patients with mild neuropsychiatric symptoms.

However, 15 out of 18 (72%) of patients without NPSLE showed normal SPECT scan. None of the healthy controls demonstrated perfusion defects. Our results are similar to that of ***Handa et al., 2003*** who found perfusion defects on SPECT in 8/10 patients with NPSLE, while only 1/10 lupus patients without clinical NP involvement and none of the healthy controls demonstrated perfusion defects. Abnormalities in cerebral perfusion in SLE patients without NPSLE may be due to the long-term use of steroids and/or SPECT may be a very sensitive detector of subclinical NPSLE ***(Nossent et al.,* 1991; *Falcini et al., 1998 and Sabbadini et al., 1999)*** that could progress to severe NPSLE ***(Falcini et al., 1998)***, however this needs a follow-up study of longer duration for a larger number of patients to conclude.

Since the territory of middle cerebral artery (MCA) is at higher risk of cerebral vasculopathy than other territories ***(Mitchell et al.,* 1994)**, the 3 most common hypoperfusion areas found on SPECT scan in our study were frontal (10 out of 11, 91%), parietal (7 out of 11, 64%) and temporal (6 out of 11, 55%) lobes which are under territory of MCA. Our results are similar to ***Colamussi et al. (1*995) *and Kao et al. (1999b),*** who found multiple areas of hypoperfusion especially in the territory of MCA, however with more involvement of the parietal lobes. Also, ***Lin et al., 1997*** found that parietal, frontal, and temporal lobes were the most common areas of CNS involvement, with 95.6%, 56.5% and 56.5% involvement respectively in patients with major NPSLE; and 80.7%, 65.3% and 46.1% involvement respectively in patients with minor NPSLE. Other studies found that hypoperfusion in the posterior cingulate gyrus and thalamus was associated with the severity of psychiatric symptoms ***(Oda et al., 2005)***. It is often suggested in these studies that correlations between anatomic location of perfusion defects or the pattern of uptake defect and clinical symptoms were not evident, due to limited number of patients ***(Rubbert et al., 1993)***. In our study, one of the two psychotic patients has shown focal left frontal region perfusion defect, this is in agreement with what ***Kovacs et al. (1995)*** suggested that SLE patients with psychosis displayed hypofrontality previously described with schizophrenia.

The observation of both diffuse and focal CNS involvement in SLE has led us, as other researchers, to hypothesize that there are several pathogenic mechanisms in NPSLE, such as microvascular damage, small-vessel vasculopathy and autoantibody-mediated neuronal cell injury ***(Devinsky et al., 1988; Hanly et al., 1992; Denburg & Behmann, 1994)***.

It was found that SPECT documented subtle and multiple abnormalities not detected by conventional imaging technique (i.e., CT scan). This may be due to the fact that CT scan can reveal morphologic alteration in the brain but SPECT was able to detect functional changes before structural damage occur ***(Reiff et al., 1997; Falcini et al., 1998)***. On the other hand, SPECT was less sensitive than EEG in detecting seizures and this may be due to transient nature of NPSLE particularly when it comes to seizures evaluation ***(Rubbert et al., 1993)***. However, other studies found that SPECT in patients with focal EEG abnormalities showed more hypoperfused areas than did SPECT of patients with diffuse EEG abnormalities, although the difference was not statistically significant ***(Colamussi et al., 1995)***.

Especially when anti-neuronal antibodies are responsible for CNS involvement, usually there is no structural damage but only cellular dysfunction which is reversible and this may have specific predilection sites ***(Aref et al., 1992)***. The transient nature of CNS involvement may affect sensitivity of SPECT ***(Falcini et al., 1998)***, hence it is possible that sensitivity of SPECT depends on timing of scanning in relation to the onset and termination of seizure attacks. Unfortunately, true ictal studies with HMPAO are nearly impossible to obtain, because this compound is stable in vitro leading to delay between seizures onset and scanning of about 5 – 20 minutes ***(Devous & Leroy,* 1989)**.

Impairment of cognitive function was present in 9 (30%) patients, 7 of them had major CNS affection and two (3.33%) had only minor NPSLE. These results are in agreement with ***Monastero et al. (2001)***, who found cognitive dysfunction in 26.9% of his sample. Also, ***Waterloo et al. (2002)*** suggested that cognitive dysfunction appears to be more common than previously thought, but its clinical significance and prognostic implications remain unclear. Other studies show a high prevalence of low-level cognitive dysfunctions, whose prevalence reaches 81% ***(Ainiala et al., 2001)***. More recently, ***Denburg & Denburg (2003)*** concluded that cognitive dysfunction has now been accepted as a bona fide manifestation of NPSLE.

Interestingly, (50%) of patients with long-standing disease (> 5 years) showed cerebral blood flow abnormalities, with diffuse uptake defects. This finding supports the notion that cerebral vasculopathy arises during the course of the disease and although it is often subclinical, it leads to cerebral blood flow disturbances in a substantial proportion of patients ***(Rubbert et al.,* 1993)**. These findings are consistent with data from autopsy studies suggesting that subclinical CNS disease may occur in a considerable proportion of SLE patients. So, cerebral lesions have been detected in absence of previous neuropsychiatric symptoms ***(Harris & Huges, 1985)***.

Major psychiatric manifestations were common in our sample. Depression was found in five patients (16.67%), however, other studies found higher rates of mood disorders that reached 43% ***(Ainiala et al., 2001)***. It is worth mentioning that the three patients who developed coma and died had major psychiatric manifestations: one of the patients presenting with cerebrovascular accident, seizures as well as organic mood (affective) disorder, organic depressive disorder (severe depression), another one with cerebrovascular accident as well as organic mood (affective) disorder, organic depressive disorder (severe depression), and the third had organic delusional (schizophrenia-like) disorder. On the other hand, one of the patients started by coma and recovered and she had cerebrovascular accident, seizures as well as organic mood (affective) disorder, organic depressive disorder (moderate depression). This can be explained by the negative effects of depression on the immune system which might lead to aggravation of SLE symptoms and/or death. ***Karassa et al. (2003)*** studied the files of 300 patients with SLE. They found that all those attempting suicide had a history of NPSLE presenting with depression, which forms another important cause for the increased mortality rate in these patients.

In general mortality was high in our sample of patients. So, three patients with major NPSLE (i.e., 42.86%) as compared to one patient without NPSLE (i.e., 5%) and none of the patients with minor NPSLE were dead by the end of the study. The difference was statistically significant ($P<0.05$) among the three groups. This is in agreement with what was suggested in earlier studies that NPSLE was a predictor of high mortality rate ***(Jonsson et al., 1989).***

Several mechanisms including immunomediated vasculopathy and neuron reactive autoantibodies ***(How et al.,* 1985)** have been implicated in the pathogenesis of CNS involvement. In our study 100% of patients with CNS affection had anti-P antibodies, yet this proportion was not significantly different ($P>0.05$) in those with and without CNS affection. However, we found a significant correlation ($P<0.05$) between SPECT findings and anti-P-antibodies. Data suggest a role for such antibodies might be presumed in CNS lupus. Also, ***Kao et al., (1999a)*** found that 5 patients out of the 12 with NPSLE had anti-P-antibodies and psychosis/depression. More recently, ***Eber et al. (2005)*** found that several autoantibodies may play a role in the pathogenesis of psychiatric complications of SLE, particularly antibodies against ribosomal P-proteins (anti-P). These autoantibodies have been suggested to be specific markers of the psychiatric manifestations of SLE. The reported prevalence of anti-P is highly variable in SLE patients and is dependent on different ethnic backgrounds, sensitivity, specificity of the assays employed for autoantibody detection, and the time at which sera were analyzed in relation to clinical events. Some studies have confirmed the hypothesis of an association of anti-P antibodies with psychiatric manifestations of neuropsychiatric SLE (NPSLE), while others have disputed this relationship. Other investigators studied anticardiolipin antibodies which had been related to various thrombotic events as well as cerebral abnormalities in SLE ***(Levine & Welch, 1987)***, they did not find any correlation between anti cardiolipin and SPECT scan findings ***(Nossent et al., 1991; Kovacs et al., 1995; and Falcini et al., 1998).***

On the other hand, our study found no significant association between the occurrence of NPSLE and the overall disease activity. This supports the hypothesis that CNS involvement in SLE is not simply a reflection of systemic disease, and evidence of disease activity in other organs is not always present ***(Sibley et al., 1992)***. However, other studies found that cerebral hypoperfusion detected by SPECT is related to clinical activity ***(Lopez-Longo et al., 2003)***. Thus, accurate diagnosis of NPSLE is an important clinical dilemma, as treatment with high-dose glucocorticoids with or without cyclophosphamide is appropriate in these conditions whether there is evidence of other systemic disease activity or not ***(Navarrete & Brey, 2000)***.

Prolactin serum hormone level was found to be ≥ 19.1 ng/ml (i.e., hyperprolactinemia) in 9 patients (30%). These results were found to be in agreement with other studies who found that 20-30% of SLE patients have hyperprolactinemia ***(Jimena et al., 1998; Walker & Jacobson, 2000; Jara et al., 2001)***. Also, hyperprolactinemia was found to have a significant statistical association ($P<0.05$) with CNS manifestations as well as with SPECT findings in our study. The interrelationship between prolactin and the immune system have been elucidated in the last decade, opening new horizons in the field of immunoendocrinology. Prolactin is secreted not only by the anterior pituitary but also by many extra-pituitary sites including the immune cells. It serves as an immunomodulator involved in lymphocyte survival, activation, and proliferation, and is, in effect, a cytokine. Prolactin receptors are distributed throughout the immune system and are included as members of the cytokine receptor superfamily ***(Vera-Lastra et al., 2002)***. There is increasing data implicating prolactin in autoimmunity, and specifically in SLE. Hyperprolcatinemia was found to be common in patients with SLE and several clinical reports have suggested that prolactin plays an important role in its pathogenesis ***(Mendez et al., 2004; Takizawa et al., 2005)***. Although, many studies found an increased level of prolactin in SLE patients ***(Vera-Lastra et al., 2003; Kramer et al., 2005)***, yet studies on the relation of prolactin level to the NPSLE has been scarce to date.

Our longitudinal data showed clinical recovery and amelioration of perfusion deficits in some patients, improvement in those patients can be attributed to increasing the doses of steroids or starting immunosuppressive therapy. Also, some patients showed the same findings in their SPECT scan, other showed more deterioration in their SPECT scan. These results are in agreement with what was found by ***Zhang et al. (2005)***, who has concluded that SPECT is more sensitive than MRI in revealing damage in diffuse CNS-SLE, and is useful in follow-up, especially for monitoring disease severity and guiding treatment. Also, ***Sun et al., 2004*** found that HMPAO-SPECT is a logical and objective tool for measuring the effects of methylprednisolone pulse therapy in SLE patients with brain involvement by determining changes in rCBF.

This difference in outcome may be explained by two different mechanisms involved in pathogenesis of CNS lupus; the first one is neuron reactive autoantibodies, which has a good prognosis and the other one is vasculitis which carries a bad prognosis usually with renal affection ***(Aref et al.,* 1992)**. So bad prognosis in those patients may not only be explained by CNS affection, but the affection of other systems especially renal affection.

Despite the fact that this study is one of the few that were longitudinal focusing on SPECT use as a diagnostic as well as a prognostic tool in NPSLE, yet it has some limitations: 1) its small sample size, this problem has faced most of the researchers who had worked on the same population; 2) although visual interpretation of SPECT results may sometimes be superior to semi-quantitative analysis, yet some subtle changes may be overlooked; 3) the short duration of the follow-up study (only 6 months).

As it is crucial to exclude secondary causes of the presenting symptoms in any patient with suspected NPSLE, our results suggest that SPECT imaging is a sensitive tool for the diagnosis of CNS involvements in SLE. While the meaning of perfusion deficits in patients without neuropsychiatric symptoms remains to be clarified, the domain of SPECT as a diagnostic tool may lie in the early detection of brain perfusion defects in patients with clinical symptoms such as headache and cognitive dysfunction. SPECT scan could therefore be helpful in substantiating the clinician's suspicion of an incipient CNS involvement. It was also found that follow-up SPECT findings were correlated with changes in neuropsychiatric symptoms. So, it might be promising as a prognostic tool in NPSLE that can be used as an activity marker that represents the activity of cerebral involvement and its response to different treatments. Whether therapeutic decision should be based on our findings, additional larger, longitudinal studies to determine the significance of SPECT alteration over the long-term course of disease need to be performed. Last but not least, it can be suggested that the clinical presentation, serologic tests and neuroimaging techniques should be combined to support the diagnosis of NPSLE.

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# Psychiatric Morbidity and Somatic Symptoms in Patients with Functional Dyspepsia: A Comparative Study with Duodenal Ulcer Patients

*Elsayed O., El Adl T. Asal. A. A. and Shahda M.*

## Abstract

Patients with functional dyspepsia (FD) would have a greater prevalence of treatable psychiatric disorders, higher scores on measures of psychiatric symptomatology and characteristic symptoms distinguishing them from those with duodenal ulcer (DU). The aim of the work is to study the prevalence of psychiatric disorders and somatic symptoms in patients with functional dyspepsia and in comparison to those of duodenal ulcer disease. We selected 100 consecutive FD patients and the same number of DU patients at their routine consultation at the outpatient's clinic of internal medicine of private general hospital at Abu Dhabi; UAE. Patients were subjected to full history, complete clinical examination, laboratory investigations, esophagogastroduodenoscopy and psychiatric evaluation through General Health Questionnaire (GHQ), Hospital Anxiety Depression Scale (HADS) and Structured Psychiatric Interview (PSE10). Patients with functional dyspepsia were significantly younger, more likely to be females, less tendency to smoke and use alcohol, had more frequent dyspeptic symptoms, a longer disease history and lower incidence of H.pylori infection than duodenal ulcer patients. Psychiatric morbidity was significantly higher in FD patients than DU patients (65% compared to 26%). Prevalence of psychiatric disorders was as follow: somatoform disorders 36%, mixed anxiety depressive disorder 21%, generalized anxiety disorder 17%, and depressive episode 4% in FD patients. As regard DU patients; somatoform disorders 8%, mixed anxiety disorder 10% and generalized disorder 8%. Using stepwise logistic regression model, it has been shown that, somatoform autonomic dysfunction and anxiety symptoms of (HADS) were independently associated with functional dyspepsia and the best predictors of diagnosing functional dyspepsia or duodenal ulcer. Psychiatric disorders are strongly associated with functional dyspepsia that warrants psychiatric intervention that may benefit FD patients specially those with chronic symptoms. Introduction

## Introduction

.Functional dyspepsia (FD) is considered a heterogeneous disorder with different pathophysiological mechanisms, contributing to the symptom pattern. The Room II committee proposed that subdividing patients FD patients with predominant pain versus discomfort might identify subgroups with homogenous clinical properties (Karamanolis et al., 2006). The term non ulcer dyspepsia reflects the previously dominant viewpoint that dyspepsia without ulcer represent, a

Functional gastrointestinal (GI) disorders such as the irritable bowel syndrome (IBS) and non ulcer dyspepsia (NUD) are characterized by chronic symptoms referable to the gastrointestinal tract in the absence of any biochemical or structural explanation (Sanfit and Jones, 2005). The patients with symptoms indicative of ulcer, but without evidence of ulcer, based on upper endoscopy, are given the diagnosis of non ulcer dyspepsia or functional dyspepsia psychiatric disorders, higher scores on measures of psychiatric symptomatology and characteristic somatic symptoms distinguishing them from patients with duodenal ulcer.

## Aim of the work:

The aim of this work was to study the prevalence of psychiatric disorders and somatic symptoms in patients with functional dyspepsia in comparison to those of duodenal ulcer disease.

## Subjects &Methods

During one year period from (May 2005 to April 2006), one hundred consecutive patients with functional dyspepsia (FD) and the same number with those of duodenal ulcer (DU), were studied at their routine consultation at the outpatient's clinic of internal medicine of private general hospital at Abu Dhabi, UAE. All were Arab (local and non local). Patients were directly invited by the authors to participate in the study; they were informed that the objective was to assess the possible relationship between psychiatric disorders and upper gastrointestinal complaints. All patients provided informed consent after receiving a full explanation of the nature and protocol of the study. The study protocol was approved by the ethics committee of the hospital.

Consecutive patients with endoscopically verified duodenal ulcer were included in the study as a comparative group because of similarities of symptoms. Dyspeptic patients without any positive endoscopical findings and fulfill the Room II criteria for FD (Talley et al., 1999), were recruited to the FD group. The criteria for inclusion were: at least 3 months (within 1 year) of subjective, persistent or recurrent complaints of epigastric pain or discomfort, special, more peaceful course of ulcer disease. However, repeated observation of functional dyspepsia patients show a low propensity of ulcer development (Vakil, 2002). Hypersecretion of gastric acid and the bacteria Helicobacter pylori which seem to be major etiological factors in duodenal ulcer (DU), do not seem to be important in functional dyspepsia (Talley and Quan, 2002). The cause of non ulcer dyspepsia (NUD) remains essentially unknown, but psychological factors have been implicated. For example, patients with NUD reported more life stress and psychological distress than healthy controls in clinic-based studies (Locke et al., 2004). German investigators reviewed, with meta analytic methods, observational studies on the association of FD with anxiety and depression. This association was established, with more patients with FD having major depression or any anxiety disorder than either healthy controls or patients with similar upper abdominal symptoms of known organic origin. The amount of self-reported depressive symptoms was not different between patients seeking medical care for their complaints and those who did not consult, but the degree of anxiety was higher in consulters than in non consulters (Henningsen et al., 2003). In support of these data are the results of a nested case-control study in a random community sample in the United States, showing that psychosocial factors, particularly somatization, interpersonal sensitivity, and total life event stress, were associated with FD (Locke et al., 2004). Also, depressive symptoms were found to be quite common in patients with FD (Jones et al., 2005).

## Hypothesis and Aim of the Work:

Patients with functional dyspepsia would have a greater prevalence of treatable from a formal psychiatric examination, performed to make a DSM-IV or ICD10 diagnosis and 4) information on recent psychiatric symptoms, obtained through General Health Questionnaire (GHQ) ,Hospital Anxiety Depression Scale (HAD). Psychiatric diagnoses were assessed according to ICD10 through structured psychiatric interview: present state Examination (PSE10).

**General Health Questionnaire (GHQ):**

The general health questionnaire is the most widely used screening test to detect psychiatric disorders in medical practice and measures possible prevalence of non psychotic psychiatric disturbances, especially anxiety and depressive disorders. We made use of the short GHQ 12 version in which each of the 12 items with a 4 answering categories was scored on a bimodal response scale resulting in a score ranging from( 0 to 12). A cut-off score of (5-6) was used to discriminate possible psychiatric cases (score ≥ 6) and non cases (scores ≤5), which according to a GHQ evaluating study shows a positive and negative predictive value of 71% and 78% respectively (Hermert et al., 1995). All patients completed the Arabic version (El-Rufaie and Daradkeh, 1996).

**Hospital Anxiety and Depression Scale (HADS):**

The Hospital Anxiety and Depression Scale (HADS) were originally developed for use in hospital settings, as the name suggests. It was designed as a self-completed questionnaire to assess patients' anxiety and depression whilst in in-patient care according to two sub-scales. The Anxiety and Depression scales, both comprise 7 questions rated from a score of (0 to 3) nausea, bloating or heartburn. The discomfort from the upper abdomen had to be the main abdominal complaint.

General exclusion criteria were: planned or previous surgical treatment (proximal gastric vagotomy or gastric resection), serious mental disorder, other somatic disorders requiring treatment, use of non-steroidal anti-inflammatory drugs (NSAID) or proton pump inhibitors or antibiotics and alcohol or drug abuse. In addition, FD patients with verified duodenal ulcer within the last 3 years, gallstones or esophagitis were excluded. Also, patients with indigestion due to heart, liver, pancreatic diseases or gastrointestinal malignancy were excluded.

***Tools and Methods of Assessment*:** Medical Examination: The functional dyspepsia and duodenal ulcer patients were medically examined by gastroenterologist (the author); the medical examination included a detailed medical history including dyspeptic symptoms, smoking and alcohol., coffee, tea and use of medications, clinical examination, abdominal ultrasonography, bed side laboratory investigations and H.pylori rapid urea breathe test (Chen et al., 2000) and Olympus GIF-XQ260 fibroptic upper gastrointestinal endoscopy.

**Psychiatric Examination:**

All patients were interviewed by a psychiatrists (the authors) blinded to the result of upper gastrointestinal endoscopy. During this interview, the following information was elicited: 1) demographic data 2) data on past psychiatric history including; previous psychiatric hospitalizations or visits to professionals; use, kinds and efficacy of psychotropic drugs and suicide attempts 3) information therefore based on a process of matching the respondent's behavior and description of subjective experiences against the clinical definitions provided in the glossary of the SCALE (World Health Organization, 1992).

### *Statistical analysis:*

All the data were recorded on investigative report form. These data were transferred to IBM card, using IBM compatible computer with statistical program (Statistical package for Social Sciences): SPSS for windows release 10.00 to obtain results.

Results:

### Sociodemographic factors:

There was an overall highly significant group differences in age ($p<0.05$) owing to being FD patients younger than DU patients. FD patients were more likely to be females (61%vs 39%), while women /men ratio in DU patients (47%vs 53%). Beyond this, there were no significant differences between the groups in socio demographic factors (Table1).

Life style factors: there was significant group difference in smoking. Patients with FD smoked less than DU-patients ($p<0.05$) .There was also a significant group difference in alcohol consumption ($p<0.05$), FD patients consumed significantly less alcohol compared to DU-patients.

There was a significant group difference in irregular meals, 39% of FD patients had irregular meals which was significantly more than the DU patients (25%) ($p<0.05$) (Table 2).

History and symptoms differences: There was a significant difference due to duration of dyspeptic complaints between FD and depending on the severity of the problem described in each question. The two sub-scales can also be aggregated to provide an overall anxiety and depression score. The anxiety and depression scores are categorized as below: Aggregate Score: (0-7) Normal, (8-10) Mild, (11-14) Moderate and (15-21) Severe (Snaith and Zigmond, 1994) .All patients completed the Arabic version of HADS (El-Rufaie and Absood, 1995)

### Present State Examination 10th revision (PSE10) (WHO, 1992):

It is a part of the SCAN system (Schedule for Clinical Assessment in Neuropsychiatry), which is a set of instruments and manuals aiming at assessing, measuring and classifying the psychopathology and behavior associated with the major psychiatric disorders of adult life. The SCAN text has 3 components; the tenth edition of the Present State Examination (PSE10), the Item Group Checklist (IGC) and the Clinical History Schedule (CHS). PSE 10 itself has two parts: part I covers somatoform, dissociative, anxiety, depression, and bipolar disorders and problems associated with eating, alcohol and other substance use disorders. Part II covers psychotic and cognitive disorders and observed abnormalities of speech, affect and behavior.

The central Principle of the PSE is that the interview, although substantially structured, retains the features of a clinical examination. The aim of the interviewer is to discover which of a comprehensive list of phenomena have been present during a designated period of time and with what degree of severity. The examination is score of 0 (0 -5). As regard DU patients 26% where considered as psychiatric cases whereas 74% showed no psychiatric disorders. FD patients scored significantly higher on Hospital anxiety depression scores than DU patients (table 4).

Table 5 shows the frequency of psychiatric disorders among both groups of patients, where it was found that: among FD patients 36% of them met the criteria for somatoform disorders (somatoform autonomic dysfunction 16%, somatization disorder 8% and hypochondriasis 12%), compared to 8% of DU patients (somatoform autonomic dysfunction 3%; somatization disorder 2% and hypochondriasis 3%) with statistical significant difference (p< 0.05); depressive episodes occurred only in 4% of FD patients. This table also shows that, mixed anxiety depression disorder occurred in 21% of FD patients compared to 10% of DU patients and generalized anxiety disorder occurred in 17% of FD patients, compared to 8% of DU patients with statistical significant difference (p< 0.05). Also, it was found that in 13% of FD patients, somatoform disorders were co morbid with mixed anxiety depressive disorders.

**The result of logistic regression analysis:**

Using stepwise logistic regression analysis ,it has been shown that ,while the initial model contained 17 variables; including : sex, life style factors ,dyspeptic symptoms and psychological measures; the final model included only 2 variables as best predictors of diagnosing functional dyspepsia or duodenal ulcer , the presence or absence of somatoform autonomic dysfunction and anxiety symptoms of HADS. The overall predictability of the model was found to be 87.5% (Table 6).

DU patients , each episode seemed to last longer for the FD patients , the mean duration for the actual episode of dyspeptic complaints being 8 months for FD patients and 5 months for the DU patients (p< 0.05). Epigastric pain was reported by 84% of DU compared to 73% of FD patients with no significant difference (p>0.05). It was significantly frequently severe, occurred at night, and in clusters (episodic) in DU than FD patients (p≤0.05). Pain relief by food was significantly more often reported by DU (48%) than by those with FD patients (32%) (P< 0.05), whereas pain provoked by food was significantly more frequent in FD patients (45%) than in DU patients (31%) (p<0.05). Otherwise, no significant difference in other pain characters. As regards other dyspeptic symptoms: bloating, postprandial fullness and early satiation were significantly more frequent in FD than DU patients (p≤ 0.05). Otherwise no significant difference in other dyspeptic symptoms (Table 3).

As regard the result of H. pylori breath test, it was positive in 48% of DU patients compared to only 12% of FD patients, with highly statistical significant difference (p<001). Also it was found that 12% of FD patients reported history of treatment of anxiety and/or depressive disorders compared to 7% of DU patients and 12% of FD patients was under psychotropic medications (antidepressants and benzodiazepines), compared to 5% of DU patients with no statistical significant difference (p>0.05).

Psychological measures: According to the GHQ cut-off score, 65% of FD patients were considered as psychiatric cases with a median range GHQ score of 8 (6–12), whereas 35% of patients showed no psychiatric disorders , with a median GHQ

**Table (1): Sociodemographic characteristics of the studied groups:**

| Patients<br>Variables | FD Patients (n=100) | DU Patients (n=100) | Test | P |
|---|---|---|---|---|
| Age(years): | | | | |
| Mean | 33.55 | 43.44 | t= -14.373 | 0.000* |
| ± SD | 5.8 | 3.7 | | |
| Sex: No (%): | | | $X^2$ | |
| Males | 39(39%) | 53(53%) | 3.945 | |
| Females | 61(61%) | 47(47%) | | 0.05* |
| Marital status: | | | | |
| Single | 22(22%) | 16(16%) | $X^2$ | |
| Married | 57(57%) | 62(62%) | 1.388 | 0.85 |
| Divorced | 10(10%) | 9(9%) | | |
| Widowed | 7(7%) | 8(8%) | | |
| Separated | 4(4%) | 5(5%) | | |
| Occupation: | | | | |
| Active remunerated | 60(60%) | 56(56%) | $X^2$ | 0.83 |
| Active non remunerated | 19(19%) | 20(20%) | 0.364 | |
| Inactive | 21(21%) | 24(24%) | | |
| Education: | | | | |
| Primary | 12(12%) | 13(13%) | $X^2$ | |
| Preparatory | 10(10%) | 10(10%) | 0.886 | 0.927 |
| Secondary | 37(37%) | 38(38%) | | |
| University | 34(34%) | 35(35%) | | |
| Postgraduate | 7(7%) | 4(4%) | | |

Active non-remunerated: student & housewife Inactive: retired & unemployed
*Significant P≤ (0.05)

**Table (2): Life style factors:**

| Patients<br>Factors | FD Patients (n=100) | DU Patients (n=100) | Test | P |
|---|---|---|---|---|
| Smoking : | | | | |
| Never | 48(48%) | 31(31%) | $X^2$ | 0.03* |
| Formerly | 15(15%) | 21(21%) | 6.82 | |
| Current | 37(37%) | 48(48%) | | |
| | | | | 0.05* |
| Alcohol use | 5(5%) | 13(13%) | $X^2$=3.907 | |
| Irregular meals | 39(39%) | 25(25%) | $X^2$=4.504 | 0.05* |

* Significant (p≤0.05

**Table 3): Dyspeptic symptoms in FD and DU Patients:**

| Patients Symptoms | FD Patients (n=100) | DU Patients (n=100) | test | P |
|---|---|---|---|---|
| Duration of symptoms (in months): Mean ±SD | 8.14 ±11.29 | 5.12 ±1.83 | T= 0.264 | 0.009* |
| Pain: | | | | |
| Epigastric | 73(73%) | 84(84%) | $X^2$=3.585 | 0.06 |
| Frequently severe | 37(37%) | 51(51%) | $X^2$= 3.977 | 0.05* |
| Relieved by food | 32(32%) | 48(48%) | $X^2$=5.333 | 0.02* |
| Relived by antacids | 73(73%) | 66(66%) | $X^2$=1.156 | 0.28 |
| provoked by food | 45(45%) | 31(31%) | $X^2$ 4.160 | 0.04* |
| occurs at night | 32(32%) | 50(50%) | $X^2$ 6.697 | 0.01* |
| cluster(episodic) | 34(34%) | 48(48%) | $X^2$ 4.051 | 0.04* |
| Anorexia | 35(35%) | 32(32%) | $X^2$= 0.202 | 0.7 |
| Vomiting | 30(30%) | 35(35%) | $X^2$= 0.57 | 0. 5 |
| Bloating | 50(50%) | 35(35%) | $X^{2=}$ 4.604 | 0.03* |
| Belching | 59(59%) | 50(50%) | $X^2$= 1.633 | 0.2 |
| Heart burn | 28(28%) | 40(40%) | $X^2$= 3.209 | 0.07 |
| Post prandial fullness | 53(53%) | 39(39%) | $X^2$ = 3.945 | 0.05* |
| Early satiation | 50(50%) | 36(36%) | $X^2$ = 3.998 | 0.05* |

* Significant: ($p \leq 0.05$)

**Table (4): Hospital Anxiety Depression Scores (HAD) among both groups of patients:**

| Patients Scores | FD Patients (n=100) | DU Patients (n=100) | test | P |
|---|---|---|---|---|
| HAD depressive scores: No of Patients (%) | | | | |
| Normal | 35(35%) | 74(74%) | | 0.000 * |
| Mild & Moderate | 40(40%) | 16(16%) | $X^2$=30.668 | |
| Severe | 25(25%) | 10(10%) | | |
| HAD anxiety scores: | | | | |
| Normal | 35(35%) | 74(74%) | | |
| Mild & Moderate | 45(45%) | 12(12%) | $X^2$=34.118 | 0.000 * |
| Severe | 20(20%) | 14(14%) | | |

*Highly Significant ($p < 0.01$)

Normal (0-7), Mild (8-10), Moderate (11-14), Severe (14-21)

**Table (5): Prevalence of ICD10 Psychiatric disorders among both groups of patients:**

| Patients<br>Disorders | FD Patients (n=100) | DU Patients (n=100) | Test | P |
|---|---|---|---|---|
| Depressive episode | 4(4%) | 0(0%) | $X^2$ 4.082 | 0.04* |
| Mixed anxiety depressive disorder | 21(21%) | 10(10%) | $X^2$ 4.619 | 0.03* |
| Generalized anxiety disorder | 17(17%) | 8(8%) | $X^2$ 3.703 | 0.05 * |
| Somatization disorder | 8(8%) | 2(2%) | $X^2$ 3.789 | 0.05 * |
| Hypochondriasis | 12(12%) | 3(3% | $X^2$ 5.838 | 0.02 * |
| Somatoform autonomic dysfunction | 16(16%) | 3(3%) | 9.828 | 0.002 * |

* Significant :( p≤ 0.05).

**Table (6): The Results of Logistic Regression Analysis:**
**Final Logistic Regression Model:**

| Variables | B | SE | Walds't' | P | Odds ratio |
|---|---|---|---|---|---|
| Somatoform autonomic dysfunction: | - 5.6 | 1.2 | 23.4 | 0.000 * | 0.004 |
| Anxiety scores: | - 2.4 | 0.5 | 22.8 | 0.000 * | 0.09 |
| Heart burn: | 11.2- | 16.8 | 0.4 | 0.51 | 0.000 |
| Early satiation: | 9.8 | 16.8 | 0.3 | 0.56 | 6.8 |
| Constant: | 6.5 | 1.3 | 25.2 | 0.000 | - |

* Statistical significant at p<0.01 level Model $X^2$:114.5 p= 0.000
SE: Standard error of B B : Regression coefficient

This table shows that while the initial model contained 17 variables, the final model included only 2 variables as best predictors of diagnosing functional dyspepsia or duodenal ulcer: somatoform autonomic dysfunction and anxiety scores of (HAD). The over all predictability of the model was found to be 87.5%.

## Discussion

In spite of similar clinical symptomatology of FD and DU patients, they comprised at least two different somatic entities. The patients differ in illness history, life style factors, symptom characteristics and measures of psychiatric symptomatology and prevalence of psychiatric disorders.

### Sociodemographic characteristics of FD and DU groups:

There was an overall a significant difference between both groups regarding age and gender, as FD patients was younger and more likely to be females than DU patients. These findings were consistent with other previous studies (Hsu et al., 2002 and Pajala et al., 2005)

### Life style factors:

Smoking was found to be less common in FD group than DU group .This result was found to be consistent with other previous studies (Archimandritis et al., 1995 and Haug et al., 1994) .Many studies reported the significant role of smoking as a risk factor for peptic ulcer disease (Luo et al., 2002 and Maity et al., 2003). FD patients use alcohol significantly less than DU patients and the overall percentage in both groups were found to be small as compared to the percentage in western studies .This could be explained by cultural differences and religious attitude in our culture that alcohol is prohibited. Patients with FD had more irregular meals than DU patient. This can be a causal factor or a result of their dyspepsia.

### Dyspeptic complaints:

Patients with FD had a longer disease history and reported more frequent dyspeptic symptoms compared to patients with duodenal ulcer .This may reflect the fact that these patients have a low threshold to visceral pain and visceral hypersensitivity that is currently regarded as the mechanism responsible for both motor alteration and abdominal pain in functional bowel disorders including FD (Mahony et al., 2006). The expression of dyspeptic symptoms may also be influenced by the personality profile as neurotic patients may seek medical advise sooner and more often than those who are emotionally stable (Cecilia et al., 2004). Also, this finding could be also explained by psychological distress that affects illness behavior, where in our study we found a high prevalence of psychiatric morbidity. Cheng (2000), examined the difference in behavioral and perceptual characteristics between non consulter and consulter in FD in a Chinese population, he found that the non consulters were distinguishable by their perceptual style copying behaviors and psychological symptoms. Moreover, high level of anxiety and depression were found to be highest in consulter compared to non consulter and healthy controls.

In our study, FD patients had more bothersome postprandial fullness in upper abdomen that occurs after ordinary sized meals and several times a week as well as early satiation that prevents finishing a regular meal .This finding was found to be consistent with the study done by Camilleri et al., 2005.

Also, it was found that the incidence of H.pylori infection was significantly higher in DU patients (48%) than FD (12%).this result was consistent with many previous studies (Karamanolis et al., 2006; McColl et al., 1997 and Tally et al., 2005).

### Psychiatric co morbidity:

Our results revealed that psychiatric morbidity was significantly higher in FD patients than DU patients, where general health questionnaire screening detected 65% of psychiatric cases compared to 26% of DU patients. Also, FD patients scored significantly higher on depression and anxiety scale (HAD) than DU patients ($p<0.001$). Also, FD patients had significantly more psychiatric diagnoses on ICD10 compared to DU patients. The most common psychiatric disorders were somatoform disorders, anxiety disorders and depressive disorders. In our multiple logistic regression models somatoform autonomic dysfunction and anxiety symptoms were independently associated with functional dyspepsia suggesting that these factors may be involved in the etiopathogenesis rather than just driving health care utilization i.e. act as confounding factors.

Our results were consistent with previous studies abroad. Magni et al., (1987) in a clinical based study found that 87% of FD patients, compared to 25% of patients with organic dyspepsia, had a psychiatric diagnosis. A larger study using structured interview and psychometric tools revealed that 34% of FD patients versus 15% of DU patients had a psychiatric diagnosis; the authors also found that the psychometric test for multiple somatic complaints was the most powerful discriminating factor, followed by general psychopathology and anxiety suggesting that involvement of these factors in the causative pathway of FD (Haug et al., 1994).

In the same direction, Pajala et al (2005) reported in their study that the prevalence of mental distress among patients with functional dyspepsia and organic dyspepsia was 38% and 36.4% respectively, these findings are not consistent across studies but conflicting results may be explained by use of different sample populations.

In contrast to the latter findings, an earlier study demonstrated no statistically significant difference between functional dyspepsia and duodenal ulcer patients on various psychometric tests scores. However, elevated level of neuroticism, anxiety and depression were found in FD patients compared to controls .No explanation was offered for the lack of difference between DU and FD patients (Talley et al., 1996). Moreover, another study had demonstrated no psychological difference between people with functional bowel disorders who have not consulted a physician compared to community based health controls (Smith et al., 1990), this has engendered the association that psychosocial factors are not implicated in the etiopathogenesis of FD and irritable bowel syndrome but rather serve to motivate health care seeking.

More recently, in contrast to this dogma elevated level of psychological distress across all domains (except phobic anxiety) of the SCL-90-R ,a measure of psychological state have been demonstrated in a population based study of subjects with functional gastrointestinal disorders (functional dyspepsia and irritable bowel syndrome), inclusive of both consulters and non consulters suggesting that these factors may be involved in the etiopathogenesis rather than just driving health care utilization (Locke et al., 2004).

In our Arab culture, Abdulhafeiz et al. (2002); in a case control study investigated the relationship between functional dyspepsia, life events and mental illness, they found that psychiatric illness was significantly more in patients than the controls. Anxiety and depressive disorders dominated the clinical picture (84%) and the symptoms were of mild nature

In our study, somatoform disorders were reported in 36% of FD patients, this could be explained by the suggestion that the psychosomatic patients are assumed to have difficulties in expressing emotions verbally and to have tendency to react with different somatic complaints (Porcelli et al., 2004). Also, it has been suggested that, somatizing symptoms can be a cultural mode of expressing mental distress in ethnic groups including Arab culture. Okasha (2004); reported that depression among Egyptian patients is manifested mainly by agitation, somatic symptoms, hypochondriasis, physiological changes such as decreased libido, anorexia and insomnia, which is not characterized by early morning awakening. Egyptian patients mask their affect with multiple somatic symptoms, which occupy the foreground and the affective component of their illness recedes to the background. This may be because of the greater social acceptance of physical complaints than of psychological complaints, which are either not taken seriously or are believed to be cured by rest or extra praying. The increase in somatic symptoms can be explained by the seriousness with which people in a given culture view 'psychological stresses compared with physical illnesses.

The association of psychiatric morbidity and FD could be explained through the gut –brain axis it has become more evident that FD is a biopsychosocial disorder (Alders, 2000), in which gastrointestinal motor abnormalities, altered visceral sensation and psychosocial factors interact to generate the symptoms. The motor, sensory and secretory activities of the gut occur through the bidirectional communication between the central nervous system, the autonomic nervous system and the enteric nervous system. FD symptoms may result from deregulated interactions at any level of the brain –gut axis (Thumshirn, 2002).

Though high prevalence of psychiatric disorders in FD patients ,only small percentage (12%) were under psychiatric treatment, and also 5% of those with DU, that could be explained by lack of mental health awareness and stigma of mental illness in our culture. So efforts should be directed towards identification and management of these obstacles.

The present study has found that FD patients have more or less distinctive clinical characteristics; significantly higher prevalence of somatoform, anxiety and depressive disorders distinguishing them from DU patients. Somatoform autonomic dysfunction and anxiety symptoms were the most predictive of diagnosis and differentiating between FD and DU patients suggesting that these factors may be involved in the etiopathogenesis of FD rather than just diving health care utilization. It should be clear, however, that the model constructed in this study should by no means replace diagnostic testing, but should be considered a helpful aid for doctors as well as for patients especially when upper gastroendoscopic finding is negative and the symptoms are bothersome chronic.

Co morbid psychiatric illness in FD patients warrants treatment with conventional therapies. Available evidence suggests psychological therapies may benefit FD patients particularly those with chronic symptoms. The rationale for use of psychotropic medications in FD patients is apparent. Future studies are needed to evaluate the efficacy of antidepressants and psychotherapeutic measures in relieving sufferening of FD patients .Primary care physicians and gastroenterologists should be aware of these psychiatric disorders for early identification and management or referral to mental health professionals in some cases. Our results suggesting that functional dyspepsia and psychopathology share common pathophysiology that warrant further examination.

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# A Comparative Study of Sexual Function in Paranoid Versus Non-Paranoid Schizophrenic Patients And Its Relation To Serum Prolactin Level

*Hashem A.H., Abd El-Gawad T., Ezzat M., Assal A., Goueily T. and El Rakhawy M.*

## Abstract:

This study was undertaken to evaluate sexuality in male patients with schizophrenia. The sample was composed of 60 male in-patients with schizophrenia divided in two groups paranoid and non-paranoid. Two study groups were subjected to full psychiatric history and full sexual assessment. Positive and negative syndrome scale was applied and Serum prolactin level was done. Sexual dysfunctions were common in male patients with schizophrenia; patients with paranoid schizophrenia and patients with non-paranoid schizophrenia had a different pattern of sexual dysfunction and were affected differently with each factor.

## Introduction

Sexual activity of the patient with schizophrenia used to be so limited compared to that of normal people as to induce even psychiatrists of such high quality as Sandor Rado to believe that the patient with schizophrenia was not interested in sexual pleasure or in any pleasure at all; he was suffering from anhedonia. Other psychiatrists interpreted this lack of sexual activity to be part of the schizophrenic withdrawal, and in prepsychotic states, to be part of the schizoid personality, which seriously limited interpersonal contacts of any kind. The beginning of a schizophrenic episode was often characterized by increased sexual behavior (Arieti, 1975).

There have been few studies of sexual function and satisfaction in people with schizophrenia, and comparisons of untreated and treated patients were rare (Baldwin and Birtwistle, 1997).

That sexual dysfunction occurred in schizophrenia was not in doubt. Persistent psychosis was associated with reductions in sexual interest, activity and satisfaction (Lyketsos *et al.*, 1983). The manifest sexual relationship problems were due to lack of social skills and degeneration of social functioning, rather than to primary, structural impairment specific to schizophrenia (Verhulst and Schneidman, 1981), (Michael et al., 2006).

On other hand, equivocal results were obtained for sexual side effects of antipsychotic drugs. Antipsychotic drugs were thought to interfere with sexual functioning but the underlying mechanisms were poorly understood (Smith *et al.*, 2002), (Rajesh et al., 2006). Dopamine antagonists, such as most antipsychotics, could reduce sexual performance both directly and indirectly through inducing hyperprolactinaemia (Segraves, 1989). Sexual dysfunction was worse in patients with schizophrenia taking antipsychotic medication compared with unmedicated patients (Kockott and Pfeiffer, 1996). The prevalence of sexual dysfunction in groups treated with neuroleptics was thought to be 60% in men, with thioridazine being one of the worst culprits (Teusch *et al.*, 1995). Moreover sexual dysfunction was an important problem even with novel antipsychotic (Atmaca *et al.*, 2004). However, anti-psychotic medication had a positive effect on psychological functioning and thus allowed patients with schizophrenia to have normal sexual interest. Moreover treated and untreated male patients reported decreased sexual desire and behavior and increased rates of premature ejaculation than did controls. In a comparison with untreated male patients, depot antipsychotic treatment increased sexual thoughts and desire but also resulted in sexual dysfunction (Aizenberg *et al.*, 1995), (Diederik et al., 2006).

## Aim of the work

The aim of this work is to study the sexual dysfunction in a sample of arabic male patients with schizophrenia. It intends to clarify the frequency of sexual dysfunction among male patients with schizophrenia, differentiate between different subtypes of schizophrenia (paranoid/non-paranoid schizophrenia) regarding sexual function and to determine the underlying factors that control sexual dysfunction in male patients with schizophrenia (including socio-demographic, medication and clinical factors).

## Subjects and Methods

### A. Subjects:

30 male patients with paranoid schizophrenia and 30 male patients with non-paranoid schizophrenia were chosen from in-patient department of private psychiatric hospital in Cairo (Dar El Mokattam for mental health).

They were chosen in consecutive manner from all admitted patients from April 2003 to December 2003 (

**According to the following criteria:**

**1- Inclusion Criteria**:

- The patients were only male patients
- Age ranged from 18-60 years
- Confirming DSM-IV criteria for schizophrenia (American Psychiatric Association, 1994), by two senior psychiatrists MD qualified.
- Good abilities of reading and writing
- Oral consents was taken

**2- Exclusion Criteria**

- History of physical disorder that may share in sexual dysfunction: Hypertension, cardiovascular disease, gonadal injury and endocrinal disorder/medications
- Recent history of substance abuse
- Refusal or inability to continue.

### B. Methods:

The study conducted in in-patient department of a private psychiatric hospital in Cairo (Dar El Mokattam for mental health) using the following tools:

A detailed psychiatric sheet was done to every patient stressing in the following points:

Demographic information, sexual history, illness history, medication history, physical history and physical examination:

The patients were diagnosed according to DSM-IV criteria by the hospital staff and the diagnosis was confirmed by two senior psychiatrists, MD qualified. The Structured Clinical Interview for DSM-IV axis I disorders (SCID-I) was used in its original English form to confirm the diagnosis of schizophrenia and its subtypes and to exclude comorbidity, The sources of information were patients, family, friends, associates, health professional and medical records (First *et al.*, 1997), in addition to

Positive and Negative Syndrome Scale (PANSS) which was used in its original English form to assess schizophrenia. This is a well-validated scale for the assessment of psychotic and allied symptoms (PANSS) (Kay *et al.*, 1987).

Sexual Function was assessed using the Sexual Behavior Questionnaire (SBQ) by Macdonold el. al., (2003) serum Prolactin level expressed in ng/ml was measured for each patient using Elecsys apparatus, model 1010(simultaneously with application of SBQ), and all samples were collected at morning. The normal range for male: 1.8 – 13.7 ng/ml.

## Results

The study included 60 male patients with schizophrenia, 30 patients with paranoid schizophrenia (50%) and 30 patients with non-paranoid schizophrenia (50%) (18 patients (60%) schizophrenia undifferentiated type, 10 patients (33.3%) schizophrenia disorganized type and two patients (6.67%) schizophrenia residual type). The age of the sample ranged from 19 to 60 years (mean = 40.2 SD = ±10.39), the age at onset (which defined as the age at which patients acquired the diagnosis of schizophrenia) ranged from 15 to 42 years (mean = 24.27 SD = ±7.22) and duration of the illness ranged from 1 to 35 years (mean = 15.97 SD = ±9.95).

**Table (1)** shows that, by using t test the percentages of patients with orgasm dysfunction and patients with less frequency of masturbations among patients with paranoid schizophrenia significantly less than that among group with non-paranoid schizophrenia.

**Table (2)** shows that, the age of patients with paranoid schizophrenia with dysfunction in sexual excitement, achieve erection, orgasm and has less frequency of masturbation is significantly more than who are sexually functioning in the same areas of sexual function.

**Table (3)** shows that, sexually functioning group (in all areas) of non- paranoid schizophrenia has no significant differences from sexually dysfunctioning group (in all areas) as regard current age of patients.

**Table (4)** shows that, age at onset in patients with paranoid schizophrenia with more frequency of sexual intercourses is significantly more than the group of less frequency of intercourses, while age of the onset in group with paranoid schizophrenia with more frequency of masturbation is significantly less than the group of less frequency of masturbation.

**Table (5)** shows that, age at onset of patients with non-paranoid schizophrenia with functioning sexual satisfaction is significantly more than who have dysfunctioning sexual satisfaction.

**Table (6)** shows that, duration of the illness in desire, excitement, achieve erection and orgasm functioning groups and in the group of more frequency of intercourses among patients with paranoid schizophrenia is significantly less than that of dysfunctioning groups in the corresponding areas.

**Table (7)** shows non significant differences in duration of the illness between sexually functioning group and sexually dysfunctioning group among patients with non-paranoid schizophrenia.

**Table (8)** shows that, the duration of the hospitalization significantly longer in sexually excitement dysfunctioning group than functioning group and among who had delayed ejaculation than who has not.

**Table (9)** shows that, by using contingency coefficient, significantly more patients with hyperprolactinaemia have low frequency of sexual intercourses and sexual satisfaction dysfunction in patients with paranoid schizophrenia than patients with normal serum prolactin.

**Table (10)** shows that, by using contingency coefficient, significantly more patients with hyperprolactinaemia have sexual desire dysfunction, sexual enjoyment dysfunction and orgasm dysfunction in patients with non-paranoid schizophrenia than patients with normal serum prolactin.

There is no significant difference in duration of hospitalization between sexually functioning and sexually dysfunctioning patients among group with non-paranoid schizophrenia.

There is no significant difference between patients on typical antipsychotics and drug free patients in patients with paranoid schizophrenia as regard all areas of sexual function.

There is no significant difference between patients on typical antipsychotics and drug free patients in patients with non-paranoid schizophrenia as regard all areas of sexual function.

***Sexual Function in the Sample:***

**Table (1): Number of Patients with Sexual Dysfunction**

| **Questions** | **Paranoids** | | **Non-paranoid** | | ***p*** |
|---|---|---|---|---|---|
| | **Number** | **%** | **Number** | **%** | |
| **Q1 Desire** | 11 (total=30) | 36.667% | 14 (total =30) | 46.667% | 0.44 |
| **Q2 Frequency of intercourses/week** | 18 (total =30) | 60% | 24 (total =30) | 80% | 0.10 |
| **Q3 Frequency of masturbation/week** | 10 (total =22) | 45.45% | 15 (total =26) | 57.69% | 0.04 |
| **Q4 Excitement** | 9 (total =30) | 42.86% | 12 (total =29) | 44.83% | 0.88 |
| **Q5 Enjoyment** | 8 (total =30) | 26.67% | 8 (total =28) | 28.57% | 0.89 |
| **Q6 Satisfaction** | 12 (total =30) | 40% | 15 (total =28) | 53.57% | 0.29 |
| **Q7 Achieve erection** | 6 (total =30) | 20% | 10 (total =28) | 35.71% | 0.18 |
| **Q8 Maintain erection** | 11 (total =30) | 36.67% | 9 (total =28) | 32.14% | 0.696 |
| **Q9 Delayed ejaculation** | 4 (total =30) | 13.33% | 7 (total =28) | 25% | 0.26 |
| **Q10 Premature ejaculation** | 13 (total =30) | 43.33% | 8 (total =28) | 28.57% | 0.27 |
| **Q11 Orgasm** | 6 (total =30) | 20% | 13 (total =28) | 46.43% | 0.04 |
| **Overall (Q1, 4-11)** | 24 (total =30) | 80% | 26 (total =30) | 86.7% | 0.527 |

**Table (2): Age (In Years) of Sexually Functioning Patients and sexually Dysfunctioning Patients in Group with Paranoid Schizophrenia**

| | | **Age** | | | |
|---|---|---|---|---|---|
| | | **Mean** | **SD** | **t** | ***p*** |
| **Q1 Desire** | F (n=19) | 35.89 | ±8.99 | | |
| | D (n=11) | 41.45 | ±11.12 | 1.497 | 0.146 |
| **Q2 Frequency of intercourses/ week** | F (n=12) | 37.17 | ±8.02 | | |
| | D (n=18) | 38.44 | ±11.34 | 0.337 | 0.738 |
| **Q3 Frequency of masturbation/ week** | F (n=12) | 33.58 | ±7.97 | | |
| | D (n=10) | 41.90 | ±10.06 | 2.165 | 0.043 |
| **Q4 Excitement** | F (n=21) | 35.05 | ±8.29 | | |
| | D (n=9) | 44.67 | ±10.90 | 2.651 | 0.0.013 |
| **Q5 Enjoyment** | F (n=22) | 35.91 | ±8.15 | | |
| | D (n=8) | 43.50 | ±12.94 | 1.920 | 0.065 |
| **Q6 Satisfaction** | F (n=18) | 36.11 | ±8.00 | | |
| | D (n=12) | 40.67 | ±12.31 | 1.132 | 0.273 |
| **Q7 Achieve erection** | F (n=24) | 35.58 | ±8.75 | 2.876 | 0.008 |
| | D (n=6) | 47.33 | ±9.81 | | |
| **Q8 Maintain erection** | F (n=19) | 36.32 | ±7.65 | | 0.252 |
| | D (n=11) | 40.73 | ±13.11 | 1.171 | |
| **Q9 Delayed ejaculation** | F (n=26) | 38.00 | ±10.44 | | 0.439 |
| | D (n=4) | 34.25 | ±6.24 | 0.785 | |
| **Q10 Premature ejaculation** | F (n=17) | 40.53 | ±9.09 | | 0.105 |
| | D (n=13) | 34.54 | ±10.49 | 1.674 | |
| **Q11 Orgasm** | F (n=24) | 36.00 | ±9.39 | | 0.032 |
| | D (n=6) | 45.67 | ±9.27 | 2.261 | |
| **overall** | F (n=6) | 38.00 | ±8.74 | | 0.986 |
| | D (n=24) | 37.90 | ±10.48 | 0.018 | |

F = Functioning D = Dysfunctioning

**Table (3): Age (In Years) of Sexually Functioning Patients and Sexually Dysfunctioning Patients in Group with Non-Paranoid Schizophrenia**

| | | Age | | t | *p* |
|---|---|---|---|---|---|
| | | Mean | SD | | |
| **Q1 Desire** | F (n=16) | 41.5 | ±9.67 | 0.517 | 0.609 |
| | D (n=14) | 43.5 | ±11.51 | | |
| **Q2 Frequency of intercourses/week** | F (n=6) | 42.33 | ±9.65 | 0.026 | 0.532 |
| | D (n=24) | 42.46 | ±10.82 | | |
| **Q3 Frequency of masturbation/week** | F (n=11) | 41.72 | ±11.75 | 0.357 | 0.724 |
| | D (n=15) | 42.87 | ±10.89 | | |
| **Q4 Excitement** | F (n=16) | 40.75 | ±9.96 | 1.078 | 0.291 |
| | D (n=12) | 45.17 | ±11.69 | | |
| **Q5 Enjoyment** | F (n=20) | 43.65 | ±8.79 | 0.777 | 0.444 |
| | D (n=8) | 40.13 | ±15.07 | | |
| **Q6 Satisfaction** | F (n=13) | 45.69 | ±7.58 | 1.422 | 0.167 |
| | D (n=15) | 40.00 | ±12.57 | | |
| **Q7 Achieve erection** | F (n=18) | 42.39 | ±904 | 0.165 | 0.871 |
| | D (n=10) | 43.10 | ±13.88 | | |
| **Q8 Maintain erection** | F (n=19) | 41.79 | ±10.70 | 0.602 | 0.552 |
| | D (n=9) | 44.44 | ±11.31 | | |
| **Q9 Delayed ejaculation** | F (n=21) | 41.81 | ±10.63 | 0.703 | 0.488 |
| | D (n=7) | 45.14 | ±11.60 | | |
| **Q10 Premature ejaculation** | F (n=20) | 44.20 | ±10.53 | 1.222 | 0.233 |
| | D (n=8) | 38.75 | ±11.03 | | |
| **Q11 Orgasm** | F (n=15) | 41.93 | ±8.46 | 0.369 | 0.715 |
| | D (n=13) | 43.46 | ±13.26 | | |
| **overall** | F (n=4) | 41.25 | ±0.96 | 0.240 | 0.812 |
| | D (n=26) | 42.62 | ±11.22 | | |

**Table (4): Age at Onset (In Years) of Sexually Functioning Patients and Dysfunctioning Group with Paranoid Schizophrenia**

| | | Age | | t | *p* |
|---|---|---|---|---|---|
| | | **Mean** | **SD** | | |
| **Q1 Desire** | F (n=19) | 25.68 | ±7.50 | 0.480 | 0.635 |
| | D (n=11) | 24.27 | ±8.21 | | |
| **Q2 Frequency of intercourses/week** | F (n=12) | 28.58 | ±5.43 | 2.288 | 0.030 |
| | D (n=18) | 22.89 | ±8.20 | | |
| **Q3 Frequency of masturbation/week** | F (n=12) | 19.67 | ±4.14 | 3.520 | 0.002 |
| | D (n=10) | 28.80 | ±7.79 | | |
| **Q4 Excitement** | F (n=21) | 24.86 | ±7.30 | 0.333 | 0.742 |
| | D (n=9) | 25.89 | ±8.85 | | |
| **Q5 Enjoyment** | F (n=22) | 24.05 | ±6.86 | 1.349 | 0.188 |
| | D (n=8) | 28.25 | ±9.33 | | |
| **Q6 Satisfaction** | F (n=18) | 24.89 | ±7.13 | 0.239 | 0.813 |
| | D (n=12) | 25.58 | ±8.70 | | |
| **Q7 Achieve erection** | F (n=24) | 24.33 | ±7.44 | 1.201 | 0.240 |
| | D (n=6) | 28.50 | ±8.29 | | |
| **Q8 Maintain erection** | F (n=19) | 24.47 | ±6.48 | 0.645 | 0.524 |
| | D (n=11) | 26.36 | ±9.58 | | |
| **Q9 Delayed ejaculation** | F (n=26) | 25.96 | ±7.44 | 1.479 | 0.150 |
| | D (n=4) | 20.00 | ±8.04 | | |
| **Q10 Premature ejaculation** | F (n=17) | 26.47 | ±7.39 | 1.069 | 0.294 |
| | D (n=13) | 23.46 | ±7.95 | | |
| **Q11 Orgasm** | F (n=24) | 24.70 | ±8.32 | 0.961 | 0.350 |
| | D (n=6) | 27.00 | ±4.10 | | |
| **Overall** | F (n=6) | 28.17 | ±6.05 | 1.076 | 0.291 |
| | D (n=24) | 24.42 | ±7.94 | | |

**Table (5): Age at Onset (In Years) of Sexually Functioning Patients and Dysfunctioning Group with Non-Paranoid Schizophrenia**

| | | Age | | t | p |
|---|---|---|---|---|---|
| | | Mean | SD | | |
| **Q1 Desire** | F (n=16) | 24.25 | ±8.01 | 0.758 | 0.455 |
| | D (n=14) | 22.36 | ±5.12 | | |
| **Q2 Frequency of intercourses/week** | F (n=6) | 27.00 | ±8.00 | 1.500 | 0.145 |
| | D (n=24) | 22.46 | ±6.30 | | |
| **Q3 Frequency of masturbation/week** | F (n=11) | 22.36 | ±4.88 | 0.143 | 0.888 |
| | D (n=15) | 22.7 | ±5.47 | | |
| **Q4 Excitement** | F (n=16) | 24.69 | ±8.15 | 1.069 | 0.295 |
| | D (n=12) | 21.83 | ±5.00 | | |
| **Q5 Enjoyment** | F (n=20) | 25.00 | ±7.50 | 1.922 | 0.066 |
| | D (n=8) | 19.63 | ±3.66 | | |
| **Q6 Satisfaction** | F (n=13) | 26.30 | ±6.84 | 2.124 | 0.043 |
| | D (n=15) | 21.00 | ±6.38 | | |
| **Q7 Achieve erection** | F (n=18) | 24.61 | ±7.76 | 1.169 | 0.253 |
| | D (n=10) | 21.40 | ±5.13 | | |
| **Q8 Maintain erection** | F (n=19) | 24.26 | ±6.67 | 0.872 | 0.391 |
| | D (n=9) | 21.78 | ±7.82 | | |
| **Q9 Delayed ejaculation** | F (n=21) | 23.80 | ±7.60 | 0.445 | 0.660 |
| | D (n=7) | 22.42 | ±5.16 | | |
| **Q10 Premature ejaculation** | F (n=20) | 23.05 | ±6.05 | 0.487 | 0.630 |
| | D (n=8) | 24.50 | ±9.41 | | |
| **Q11 Orgasm** | F (n=15) | 23.13 | ±5.93 | 0.264 | 0.794 |
| | D (n=13) | 23.85 | ±8.33 | | |
| **Overall** | F (n=4) | 27.00 | ±9.02 | 1.159 | 0.256 |
| | D (n=26) | 22.81 | ±6.41 | | |

**Table (6): Duration of Illness (In Years) of Sexually Functioning Patients and Sexually Dysfunctioning Patients with Paranoid Schizophrenia**

| | | **Duration of the Illness** | | | |
|---|---|---|---|---|---|
| | | **Mean** | **SD** | **t** | ***p*** |
| **Q1 Desire** | F (n=19) | 10.05 | ±8.54 | 2.414 | 0.023 |
| | D (n=11) | 17.64 | ±8.38 | | |
| **Q2 Frequency of intercourses/week** | F (n=12) | 8.33 | ±7.19 | 2.430 | 0.022 |
| | D (n=18) | 15.83 | ±8.92 | | |
| **Q3 Frequency of masturbation/week** | F (n=12) | 13.92 | ±7.95 | 0.078 | 0.939 |
| | D (n=10) | 13.60 | ±11.13 | | |
| **Q4 Excitement** | F (n=21) | 10.05 | ±7.83 | 2.921 | 0.007 |
| | D (n=9) | 19.33 | ±8.35 | | |
| **Q5 Enjoyment** | F (n=22) | 11.73 | ±7.96 | 1.127 | 0.269 |
| | D (n=8) | 15.88 | ±11.31 | | |
| **Q6 Satisfaction** | F (n=18) | 11.06 | ±7.94 | 1.350 | 0.188 |
| | D (n=12) | 15.50 | ±10.05 | | |
| **Q7 Achieve erection** | F (n=24) | 11.13 | ±7.89 | 2.228 | 0.034 |
| | D (n=6) | 19.67 | ±10.44 | | |
| **Q8 Maintain erection** | F (n=19) | 11.68 | ±7.90 | 0.921 | 0.365 |
| | D (n=11) | 14.82 | ±10.65 | | |
| **Q9 Delayed ejaculation** | F (n=26) | 12.62 | ±8.88 | 0.335 | 0.740 |
| | D (n=4) | 14.25 | ±10.75 | | |
| **Q10 Premature ejaculation** | F (n=17) | 14.18 | ±10.13 | 0.937 | 0.357 |
| | D (n=13) | 11.08 | ±7.16 | | |
| **Q11 Orgasm** | F (n=24) | 11.17 | ±8.35 | 2.164 | 0.039 |
| | D (n=6) | 19.50 | ±8.80 | | |
| **Overall** | F (n=6) | 9.33 | ±10.05 | 1.073 | 0.292 |
| | D (n=24) | 13.71 | ±8.67 | | |

**Table (7): Duration of the Illness (In Years) of Sexually Functioning Patients and Dysfunctioning Group with Non-Paranoid Schizophrenia**

| | | Duration of Illness | | | |
|---|---|---|---|---|---|
| | | **Mean** | **SD** | **t** | ***p*** |
| **Q1 Desire** | F (n=16) | 17.19 | ±8.55 | 1.120 | 0.272 |
| | D (n=14) | 21.29 | ±11.45 | | |
| **Q2 Frequency of intercourses/week** | F (n=6) | 15.33 | ±9.93 | 1.028 | 0.313 |
| | D (n=24) | 20.04 | ±10.06 | | |
| **Q3 Frequency of masturbation/week** | F (n=11) | 18.82 | ±9.90 | 0.522 | 0.606 |
| | D (n=15) | 20.93 | ±10.42 | | |
| **Q4 Excitement** | F (n=16) | 16.13 | ±10.07 | 1.905 | 0.068 |
| | D (n=12) | 23.33 | ±9.69 | | |
| **Q5 Enjoyment** | F (n=20) | 18.70 | ±9.14 | 0.408 | 0.687 |
| | D (n=8) | 20.50 | ±13.65 | | |
| **Q6 Satisfaction** | F (n=13) | 19.62 | ±9.54 | 0.187 | 0.853 |
| | D (n=15) | 18.87 | ±11.38 | | |
| **Q7 Achieve erection** | F (n=18) | 17.78 | ±9.31 | 0.982 | 0.335 |
| | D (n=10) | 21.80 | ±12.16 | | |
| **Q8 Maintain erection** | F (n=19) | 17.63 | ±9.84 | 1.181 | 0.248 |
| | D (n=9) | 22.56 | ±11.28 | | |
| **Q9 Delayed ejaculation** | F (n=21) | 18.10 | ±10.52 | 0.988 | 0.332 |
| | D (n=7) | 22.57 | ±9.91 | | |
| **Q10 Premature ejaculation** | F (n=20) | 21.10 | ±10.13 | 1.560 | 0.131 |
| | D (n=8) | 14.50 | ±10.09 | | |
| **Q11 Orgasm** | F (n=15) | 18.67 | ±8.88 | 0.295 | 0.771 |
| | D (n=13) | 19.85 | ±12.23 | | |
| **overall** | F (n=4) | 14.25 | ±8.50 | 1.039 | 0.308 |
| | D (n=26) | 19.85 | ±10.20 | | |

**Table (8): Duration of Hospitalization (In Weeks) of Sexually Functioning Patients and Dysfunctioning Group with Paranoid Schizophrenia**

| | | **Duration of Hospitalization** | | **t** | ***p*** |
|---|---|---|---|---|---|
| | | **Mean** | **SD** | | |
| **Q1 Desire** | F (n=19) | 58.05 | ± 120.4 | 0.975 | 0.338 |
| | D (n=11) | 107.73 | ± 156.7 | | |
| **Q2 Frequency of intercourses/week** | F (n=12) | 29.08 | ± 85.97 | 1.613 | 0.118 |
| | D (n=18) | 107.2 | ± 152.98 | | |
| **Q3 Frequency of masturbation/week** | F (n=12) | 109.92 | ± 171.49 | 0.249 | 0.771 |
| | D (n=10) | 90.6 | ± 127.44 | | |
| **Q4 Excitement** | F (n=21) | 43.67 | ± 107.61 | 2.153 | 0.04 |
| | D (n=9) | 152.33 | ± 164.96 | | |
| **Q5 Enjoyment** | F (n=22) | 75.41 | ± 143.89 | 0.057 | 0.955 |
| | D (n=8) | 78.61 | ± 112.66 | | |
| **Q6 Satisfaction** | F (n=18) | 79.56 | ± 138.75 | 0.161 | 0.873 |
| | D (n=12) | 71.33 | ± 133.46 | | |
| **Q7 Achieve erection** | F (n=24) | 69.5 | ± 138.95 | 0.545 | 0.590 |
| | D (n=6) | 103.33 | ± 121.79 | | |
| **Q8 Maintain erection** | F (n=19) | 63.63 | ± 126 | 0.670 | 0.508 |
| | D (n=11) | 98.09 | ± 151.53 | | |
| **Q9 Delayed ejaculation** | F (n=26) | 56.38 | ± 106.9 | 2.198 | 0.036 |
| | D (n=4) | 205.5 | ± 231.56 | | |
| **Q10 Premature ejaculation** | F (n=17) | 94.65 | ± 159.42 | 0.853 | 0.401 |
| | D (n=13) | 52.23 | ± 93 | | |
| **Q11 Orgasm** | F (n=24) | 90.83 | ± 146 | 1.196 | 0.242 |
| | D (n=6) | 18 | ± 16.54 | | |
| **Overall** | F (n=6) | 64.83 | ± 148.53 | 0.229 | 0.820 |
| | D (n=24) | 79.13 | ± 133.91 | | |

**Table (9): Identification of the relation between serum prolactin level and sexual function in patients with paranoid schizophrenia**

| | | **Normoprolactinaemic** | **Hyperprolactinaemic** | ***C*** | ***p*** |
|---|---|---|---|---|---|
| **Q1 Desire** | **functioning** | 17 | 2 | 0.212 | 0.236 |
| | **dysfunctioning** | 8 | 3 | | |
| **Q2 Frequency of intercourses/week** | **functioning** | 12 | - | 0.343 | 0.046 |
| | **dysfunctioning** | 13 | 5 | | |
| **Q3 Frequency of masturbation/week** | **functioning** | 9 | 3 | 0.059 | 0.781 |
| | **dysfunctioning** | 8 | 2 | | |
| **Q4 Excitement** | **functioning** | 17 | 4 | 0.097 | 0.593 |
| | **dysfunctioning** | 8 | 1 | | |
| **Q5 Enjoyment** | **functioning** | 19 | 3 | 0.134 | 0.460 |
| | **dysfunctioning** | 6 | 2 | | |
| **Q6 Satisfaction** | **functioning** | 17 | 1 | 0.343 | 0.046 |
| | **dysfunctioning** | 8 | 4 | | |
| **Q7 Achieve erection** | **functioning** | 21 | 3 | 0.218 | 0.221 |
| | **dysfunctioning** | 4 | 2 | | |
| **Q8 Maintain erection** | **functioning** | 16 | 3 | 0.031 | 0.865 |
| | **dysfunctioning** | 9 | 2 | | |
| **Q9 Delayed ejaculation** | **functioning** | 21 | 5 | 0.173 | 0.337 |
| | **dysfunctioning** | 4 | - | | |
| **Q10 Premature ejaculation** | **functioning** | 14 | 3 | 0.030 | 0.869 |
| | **dysfunctioning** | 11 | 2 | | |
| **Q11 Orgasm** | **functioning** | 20 | 4 | 0.000 | 1 |
| | **dysfunctioning** | 5 | 1 | | |
| **Overall** | **functioning** | 6 | - | 0.218 | 0.221 |
| | **dysfunctioning** | 19 | 5 | | |

**Table (10): Identification of the relation between serum prolactin level and sexual function in patients with non-paranoid schizophrenia**

| | | Normopro-lactinaemic | Hyperpro-lactinaemic | *C* | *p* |
|---|---|---|---|---|---|
| **Q1 Desire** | **functioning** | 15 | 1 | 0.345 | 0.044 |
| | **dysfunctioning** | 9 | 5 | | |
| **Q2 Frequency of intercourses/week** | **functioning** | 5 | 1 | 0.042 | 0.819 |
| | **dysfunctioning** | 19 | 5 | | |
| **Q3 Frequency of masturbation/week** | **functioning** | 9 | 2 | 0.099 | 0.612 |
| | **dysfunctioning** | 11 | 4 | | |
| **Q4 Excitement** | **functioning** | 12 | 4 | 0.100 | 0.595 |
| | **dysfunctioning** | 10 | 2 | | |
| **Q5 Enjoyment** | **functioning** | 18 | 2 | 0.403 | 0.02 |
| | **dysfunctioning** | 4 | 4 | | |
| **Q6 Satisfaction** | **functioning** | 12 | 1 | 0.298 | 0.099 |
| | **dysfunctioning** | 10 | 5 | | |
| **Q7 Achieve erection** | **functioning** | 15 | 3 | 0.154 | 0.410 |
| | **dysfunctioning** | 7 | 3 | | |
| **Q8 Maintain erection** | **functioning** | 15 | 4 | 0.013 | 0.944 |
| | **dysfunctioning** | 7 | 2 | | |
| **Q9 Delayed ejaculation** | **functioning** | 16 | 5 | 0.100 | 0.595 |
| | **dysfunctioning** | 6 | 1 | | |
| **Q10 Premature ejaculation** | **functioning** | 16 | 4 | 0.055 | 0.771 |
| | **dysfunctioning** | 6 | 2 | | |
| **Q11 Orgasm** | **functioning** | 14 | 1 | 0.360 | 0.041 |
| | **dysfunctioning** | 8 | 5 | | |
| **Overall** | **functioning** | 4 | - | 0.192 | 0.283 |
| | **dysfunctioning** | 20 | 6 | | |

## Discussion

Sexuality in chronic and/or severe mental illness is not a widely researched or widely discussed topic, although there are many issues involved that are important for the clinician (Silva, 2000).

Sexual dysfunction occurs in schizophrenia is not in doubt. Both the illness (Aizenberg *et al.*, 1995) and antipsychotic medication (Kotin *et al.*, 1976) have been implicated.

This study was designed to evaluate sexual function in schizophrenic patients and to determine the possible underlying mechanisms. The main aim of this study is to assess the frequency and factors of sexual dysfunction in schizophrenic patients, comparing between paranoid and non-paranoid schizophrenic patients, the relation between psychopathology and sexual function and finally to determine the role of neuroleptic in sexual dysfunction in schizophrenic patients.

The hypothesis of this study is that people with schizophrenia report much higher rates of sexual dysfunction, and this phenomenon has multifactor aspects; such as age, age of onset, duration of illness, psychopathology, hospitalization, medication and consequent elevated serum prolactin level. This is yet another aspect of the poor quality of life led by many people with schizophrenia that should be addressed and clinicians should routinely enquire about sexual performance.

In this study, group one consisted of 30 in-patients with schizophrenia, paranoid type, and group two consisted of 30 in-patients with schizophrenia, non-paranoid types (18 patients were diagnosed as schizophrenic undifferentiated type, 10 patients were diagnosed as schizophrenic disorganized type and two patients were diagnosed as schizophrenic residual type), were diagnosed according to the DSM-IV diagnostic criteria. Patients, on medications or drug free (on admission), were included. There was no statistical significant difference among the two groups regarding the occupational level, socioeconomic status and marital status, which ensure that the two groups were matched.

The two groups underwent structured clinical interview for DSM-IV axis I disorders (SCID-I) to confirm the diagnosis of schizophrenia, positive and negative syndrome scale (PANSS) for schizophrenia to assess the psychopathology dimensions and sexual behavior questionnaire (SBQ). In addition, serum Prolactin level was measured for the two groups.

## ***Demographic characteristics:***

### 1. Age

There was no significant difference between the two groups as regard the current age.

**In paranoid schizophrenic group:**

Aging affects both performance and frequency of sexual activities; as the sexual excitement impaired and this finding is consistent with Masters and Johnson (1966) findings that, aging men require both a longer and more direct genital stimulation to achieve erection. Aging also affects erectile function as the achievement of erection was impaired and this finding is supported by findings of Smith *et al.* (2002) who found that, age was significantly correlated with erectile dysfunction ($r=0.46$, $P < 0.001$). Sense of intensity of orgasm impaired by aging, while the sexual interest does not diminish with age. As regard sexual activities, the frequency of masturbation diminished, which is consistent with Bortz *et al.* (1999) that, age correlated consistently with increased erectile dysfunction and decreased sexual activity and not consistent with Weizman and Hart (1987) that, ageing was associated with a decline in the frequency of sexual intercourse and an increase in the frequency of masturbation.

**In non-paranoid schizophrenia:**

All areas of sexual function and frequency of sexual activities are not affected by aging which is not consistent with previous studies, which is could be due to that, the effect of age on sexual function in non-paranoid schizophrenia is masked by other factors, specially the effect of psychopathology.

**2. Marital Status**:

No significant difference between both groups as regard having partner, which ensure that the two groups were matched. No significant differences between patients who had partner and patients who had not in all areas of sexual function regarding sexual performance among both groups (paranoid and non-paranoid, these result is consistent with those found by Macdonald *et al.* (2003), while patients who had partner reported significant higher frequencies of sexual intercourses than who had not among both groups (paranoid and non-paranoid), which is consistent with our culture.

***Sexual dysfunction:***

*Clinical Characteristics:*

Our results showed that, 80% of paranoid schizophrenic patients had at least one sexual dysfunction; the most common sexual dysfunction among this group was premature ejaculation (43.33%), followed by impaired sexual excitement (42.86%), sexual satisfaction (40%), sexual desire (36.7%), maintain erection (36.7%), sexual enjoyment (26.67%), achieve erection (20%) and intensity of orgasm (20%), the least sexual dysfunction in this group was delayed ejaculation (13.33%).

86.7% of non-paranoid schizophrenic patients had at least one sexual dysfunction; the most common sexual dysfunction among this group was sexual satisfaction (53.57%), followed by sexual desire (46.667%), intensity of orgasm (46.43%), sexual excitement (44.83%), achieve erection (35.71%), maintain erection (32.14%), premature ejaculation (28.57%) and sexual enjoyment (28.57%), the least sexual dysfunction in this group, as in paranoid schizophrenic group, was delayed ejaculation (25%).

These findings are supported with the findings of Macdonald *et al.* (2003) that, at least one sexual dysfunction was reported by 82% of male schizophrenic patients; had less desire for sexual intercourse (52%), were less likely to achieve an erection (52%), were less likely to maintain an erection (36%), were more likely to ejaculate too quickly (35%), and were less satisfied with the intensity of their orgasms (33%).

Patients with paranoid schizophrenia satisfied with their intensity of orgasm (all other factors were equivalents) more than non-paranoid schizophrenic patients, this difference may be, in part, due to that, Normal orgasm results from complex neural interactions and may require a degree of central processing (Dunsmuir and Emberton, 1997), which is impaired in non-paranoid schizophrenic patients more than in paranoid schizophrenic patients (Horvath and Meares, 1979)

**1. Age of the onset:**

There was no significant difference between the two groups as regard the age of the onset (which defined as the age at which patients acquired the diagnosis of schizophrenia). The age of the onset of the whole sample ranged from 15 to 42 years (mean = 24.27 SD = 7.22) which is consistent with the conventional thinking that schizophrenia is a disorder of adolescents and young adulthood; dementia praecox (Sable and Jeste, 2002). Moreover, it is consistent with Owida *et al.* (1999) who found that, the mean age of schizophrenia was 24.02± 10.57 years and with Abdel Gawad *et al.* (2000) who found that, the age at onset for male schizophrenic was 22.8 (±7.2).

**In paranoid schizophrenic group:**

There was no significant effect of age of the onset regarding sexual performance while the age of the onset affected frequency of sexual activity; early onset of schizophrenia related to lower frequency of sexual intercourses and higher frequency of masturbations, which may be, in part, due to that, premorbid social impairment (including low sexual activity) was more common in early-onset schizophrenia and there appears to be developmental continuity from premorbid impairment to negative symptoms (Hollis, 2003).

In non-paranoid schizophrenic group:

Age of the onset of schizophrenia affected sexual satisfaction; early onset of the illness related to dysfunction of sexual satisfaction, while there was no effect on frequency of sexual activity was reported.

**2. Duration of the illness:**

The duration of the illness was significantly higher in patients with non-paranoid schizophrenia than patients with paranoid schizophrenia which was supported by Beratis *et al.* (1994) who found that, the disorganized and undifferentiated subtypes were predominantly of adolescent-onset, whereas the paranoid subtype was most frequently first diagnosed in adult life and the correlation between long duration of the illness and reduction of positive symptoms (delusion and suspiciousness).

**In non paranoid schizophrenic group:**

Both sexual performance and frequency of sexual activity were affected by the duration of the illness; the sexual desire, sexual excitement, erectile function (in the form of achievement of erection) and orgasm impaired as the duration of schizophrenia increased. Moreover, frequency of sexual intercourses significantly decreased as the duration of the illness increased, which might be explained by tendency of patients with schizophrenia to be more isolated and withdrawn from social and emotional activities, during the deterioration course of the illness (Slater and Roth, 2001), and was supported by the correlation between longer duration of illness and negative symptoms(conceptual disorganization, blunted affect, poor rapport, lack of spontaneity of speech and stereotyped thinking).

**In non-paranoid schizophrenic group:**

No effect of the duration of the illness on any areas of sexual function, sexual performance and frequency of sexual activity, which could be due to that, the role of duration of the illness in this group regarding sexual function is masked by other factors, specially psychopathology.

**3. Medications:**

No significant difference between both groups regarding the medication received by both groups.

Most antipsychotic drugs have adverse sexual effects but it is difficult accurately to identify the incidence of treatmentemergent dysfunction, as disturbances can be reliably detected only from systematic enquiries made at baseline and during treatment (Baldwin and Mayers, 2003), (Gothelf et al., 2004) this may explain that, there were no differences founded between who received typical antipsychotic and who were drug free, which could be due to that, the effect of the illness itself superimposed on sexual side effects of medication.

**4. Serum Prolactin Level:**

16.7% of paranoid schizophrenic group were hyperprolactinaemic versus 20% of non-paranoid schizophrenic group, and there was no significant difference between the two groups regarding serum prolactin level.

**In paranoid schizophrenic group:**

Hyperprolactinaemic patients reported significant degree of sexual satisfaction dysfunction and low frequency of sexual intercourses.

**In non-paranoid schizophrenic group:**

Hyperprolactinaemic patients reported significant degree of sexual desire dysfunction and orgasm dysfunction which is supported with that hyperprolactinemia caused hypogonadism with suppressed LH and FSH levels and low testosterone levels. Hypogonadism caused diminished libido. Diminished libido might also reflect suppression of GnRH, as testosterone replacement was not as effective as suppression of hyperprolactinemia (Bennett and Plum, 1994), (Anna and Veronica, 2003).

Moreover, hyperprolactinaemic patients reported significant degree of sexual enjoyment dysfunction, which was another topic of sexual dysfunction due to hyperprolactinaemia, which may be explained by that, hyperprolactinaemia, was the outcome of impairing dopamine secretion or action (Bennett and Plum, 1994), (Bruno, 2006) which is a neurochemical mediator of "life's pleasures" (Wise, 1982).

**5. Duration of Hospitalization**:

There was no significant difference between both groups regarding how long they were hospitalized.

**In paranoid schizophrenic group:**

The effects of an increase in the length of stay in hospital, we found a parallel impairment in the sexual excitement as well as increase incidence of delayed ejaculation, which could be due to understimulating social environments in hospitals and the significant correlation between hospitalization and negative symptoms (Oshima *et al.*, 2003).

**In non-paranoid schizophrenic group:**

No significant effect of duration of hospitalization on sexual performance or frequency of sexual activity of this group, the effect of hospitalization could be masked by other factors.

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# The Relation between Major Depression, Plasma Cytokines and Highly Sensitive CRP

***Ezat M., Zahra A., Hassona A. and Obeah E.***

## Abstract

A little is known about the relation of plasma cytokines with psychological risk factors, such as hopelessness and severity of depressive symptoms. The present study examined the effect of depression on plasma IL-1β, IL-6 and hsCRP in a sample of 40 healthy, nonsmoking men. After an overnight fast, blood samples for plasma IL-6, IL-1β, highly sensitive C reactive protein (hsCRP) and fasting lipids were collected on the same day that the Beck Depression Inventory (BDI), Hopelessness Scale and full psychiatric sheet were administered. Plasma IL-6, IL-1β and hsCRP were determined using enzymatic-linked immunosorbent assay (ELISA). There was a significant difference between depressed patients and normal controls as regards mean scores of BDI, HS, IL-1β, IL-6 and hsCRP. There was also a significant difference between patients with mild depression and those with moderate and severe depression as regards mean scores of BDI, IL-1β, IL-6 and hsCRP. There was also a significant difference between patients with mild hopelessness and those with moderate and severe hopelessness as regards mean scores of HS, IL-1β, IL-6 and hsCRP. Patients with major depression revealed high levels of IL-1β, IL-6 and hsCRP. This makes such patients more vulnerable to cerebrovascular accidents, where elevation of plasma cytokines and inflammatory markers are considered as risk factors for myocardial infarction.

**Abbreviations:** APP = acute-phase protein;; ASCVD = atherosclerotic cardiovascular disease;; BDI = Beck Depression Inventory;; BMI = body mass index;; CHD = coronary heart disease;; CDC = Centers for Disease Control;; ELISA = enzymatic-linked immunosorbent assay;; HDL = high density lipoprotein;; IL = interleukin;; MCP = monocyte chemotactic protein;; MDD = major depressive disorder;; MI = myocardial infarction;; MRI = magnetic resonance imaging;; OTC = over-the-counter;; TC = total cholesterol;; TNF-α = tumor necrosis factor-α.

## Introduction

Major depression is viewed as a disorder that involves abnormalities in the central monoaminergic neurotransmitter system and gives rise to behavioral changes and alterations in neurohormonal pathways. It has recently been suggested that the behavioral deficits, central monoamine abnormalities, and hypothalamic–pituitary–adrenal (HPA) axis activation observed in major depression are associated with alterations in immune function, **Weisse, (1992), Connor and Leonard, (1998).**

Much of the recent work linking depression with inflammation has been prompted by the search for potential shared etiological mechanisms that might explain the striking co-morbidity between these medical illnesses and major depression **Evans, et al. (2005)**, **Kenneth and Fakhreddin, (2006).**

Evidence for increased inflammation in patients with major depression who are otherwise medically healthy have been repeatedly observed to have activated inflammatory pathways, as manifested by increased proinflammatory cytokines, increased acute-phase proteins and increased expression of chemokines and adhesion molecules, **Miller, et al, (2005), Bouhuys, et al, (2004).**

Cytokines are large (17- to 51-kD) hydrophilic molecules that are unlikely to cross the blood-brain barrier. Four major hypotheses have been proposed for the mechanism by which peripherally released cytokines communicate with the brain: 1) active transport of cytokines across the blood-brain barrier; 2) access of cytokines to the brain in areas where the blood-brain barrier is weak; 3) conversion of cytokine signal into secondary signals; and 4) transmission of cytokine signals along sensory afferents onto the relevant brain regions, **Connor and Leonard, (1998)**, **Kahl, et al, (2005).**

The "macrophage theory of depression" was proposed considering the potent brain effects of proinflammatory cytokines such as IL-1β and the association between pathological states of immune alteration and depression, increased serum concentrations of positive acute-phase proteins (C-reactive protein, haptoglobin, $\alpha_1$-antitrypsin) and increased secretion of cytokines, particularly IL-6, after in vitro induction by mitogens, particularly IL-1ß, IL-6, and interferon gamma (INF-γ), **Smith, (1991), Dantzer, (1997).**

Interleukin-1β (IL-1β) is released as part of the acute phase immune response and can directly stimulate the release of corticotrophin-releasing hormone and thus induce HPA axis hyperactivity. Major depression has been shown to be accompanied by both an acute phase immune response, including raised IL-1β production and HPA axis hyperactivity, **Owen, et al, (2001).**

C-reactive protein (CRP) was the first acute-phase protein to be described as an acute phase reactant that increases dramatically in response to tissue injury or infection. It is synthesized primarily in the liver predominantly under transcriptional control by the cytokine IL-6 and other pro-inflammatory cytokines, although other sites of local CRP synthesis and possibly secretion have been suggested, **Ross, (1999), Libby and Ridker, (1999).**

The effects of cytokines on the nervous system and the endocrine system close the loop between the brain and the immune system, which indicates that neural-immune interactions are bidirectional. IL-1β and IL-6 exert potent enhancing effects on the HPA axis by stimulating hypothalamic corticotropin-releasing hormone (CRH), **Anisman,et al, (1999), Levine,et al, (1999), Lanquillon, et al, (2000).**

An immune reaction as measured by proinflammatory cytokines is positively correlated with depressive symptoms and with the impaired feedback regulation of the HPA axis in major depression. IL-6 stimulates the HPA axis and exerts its actions on immune cells, **Anisman,et al, (1999), Colin, et al., (2003).** It has been reported that IL-1ß–induced adreno-corticotropic hormone, corticosterone, and IL-6 production is mediated by IL-1 type I receptors, **Owen, et al, (2001), Thomas, et al, (2005).**

## Methods

### Statistical methods

Continuous variables are expressed by mean and standard deviation and compared using t-student for comparison of two groups or one-way ANOVA (analysis of variance) for more than 3 groups' comparison. They are correlated to each others using Pearson correlation coefficient. P value was considered significant when less than 0.05.

### Sample

The present study was conducted between January 2005 and July 2005. Participants were divided into two groups; patient group included 20 healthy, nonsmoking males (aged 20–40 years) recruited from the psychiatry clinic at Kasr El-Ainy Hospital fulfilling the DSM-IV Axis I disorders, **Ventura, et al, (1998),** criteria for major depression (as diagnosed by a senior and a junior doctors). Control group included 20 healthy, nonsmoking males (age matched with no current or past history of psychiatric disorders). Participants with past history or current diagnosis of medical conditions that could alter plasma cytokines (e.g. asthma, allergies, arthritis, cancer or cardiovascular disease) or using antidepressant medications were excluded from the study. Two weeks preceding collection of blood samples, the participants had no acute infections or injuries and were advised not to receive any medications and over-the-counter (OTC) preparations, including daily low-dose aspirin. Informed consent was obtained before study participation.

### Procedure:

After overnight fasting for 12 hours, blood samples were collected from a forearm vein between 9:00 AM and 10:00 AM. After blood sampling, subjects completed the 21-item BDI, **Beck, et al, (1988),** and Hopelessness Scale and full psychiatric sheet was obtained with special stress on past and family history. The BDI and hopelessness scale have been reported to have good psychometric properties including adequate internal validity, good test-retest reliability, and construct validity, **Nezu, et al, (2002)**.

### BDI

The original BDI consists of 21 questions about how the subject was feeling in the last week. Each set of five possible answer choices range in increasing intensity. When the test is scored, a value of 1 to 5 is assigned for each answer. The standard cut-offs are as follows: 21-41 indicates that a person is not depressed, 42-62 indicates mild-moderate depression, 63-83 indicates moderate-severe depression and 84-105 signifies indicates severe depression, **Beck, (1972), Beck, et al, (1996), Beck, et al, (1996),**

### Beck Hopelessness Scale

This 20-item self-report instrument assesses the degree to which an individual holds negative expectations towards their future. The underlying assumption is that hopelessness can be objectively measured by defining it as a system of cognitive schemas with a common denominator of negative expectations. The scale has been used extensively with adolescents, and has been shown to have high internal consistency (KR-20 coefficient alpha = 0.93) and a relatively high correlation with clinical ratings of hopelessness The standard cut-offs are as follows: 0-8 indicates that a person has no significant hopelessness, 8-12 indicates mild-moderate hopelessness, 12-16 indicates moderate-severe hopelessness and more than 16 indicates severe hopelessness with risk of suicide, **Beck, and Weissman, (1974)**.

### Assessment of Interleukein-1 β, Interleukein-6, hsCRP and Lipids

After overnight fasting, blood was collected from anticubital vein by venipuncture. For plasma IL-1β and IL-6 and hsCRP, blood samples were collected in 7-ml pyrogen-free tubes with EDTA. Whole blood samples remained chilled for approximately 30 minutes. Blood samples were centrifuged at 3000 rpm and plasma was separated and stored at -20° C until time of assay.

Plasma IL-1β, **Dinarello, (1984),** and IL-6, **Sakamoto, et al, (1994),** levels were measured by an enzyme-linked immunosorbent assay (ELISA) kits commercially available from Bio Source Europe S.A., Belgium, using Mrx dynatech laboratories ELISA reader and concentrations were derived from a standard curve. The detectable limit for both plasma IL-1β and IL-6 was <1 pg/mL and the intra- and interassay coefficients of variation were <5% and <10%, respectively.

Plasma hsCRP, **Ridker, (2003),** levels were measured by an enzyme-linked immunosorbent assay (ELISA) diagnostic kit commercially available from DiaMed EuroGen, Belgium using Mrx dynatech laboratories ELISA reader. Samples should be diluted prior to assay. A recommended starting dilution is 1:100 with Standard A/Sample Diluent (zero Standard) prior to assay. Results for these samples must be multiplied by 100 to correct for the additional dilution.

Serum total cholesterol and HDL cholesterol, **Trinder, (1969),** were measured enzymaticaly using SENTINEL CH commercially available kit

## Results

**Table 1: Comparison between Control group and Patient group as regard mean scores of Age, BMI, Cholesterol, HDL Cholesterol, BDI, HS, IL-1β, IL-6 and hsCRP.**

| | **Control group** | **Patient group** | |
|---|---|---|---|
| | **Mean (SD)** | **Mean (SD)** | **P value** |
| **Age (yr)** | 29.0 (1) | 27.3 (1.5) | >0.05 (NS) |
| **Body mass index (kg/m$^2$)** | 23.3 (0.58) | 25.7 (3.0) | >0.05 (NS) |
| **Total cholesterol (mg/dL)** | 176.3 (15.8) | 176.7 (32.1) | >0.05 (NS) |
| **HDL cholesterol (mg/dL)** | 48.3 (8.5) | 52.3 (9.3) | >0.05 (NS) |
| **Beck Depression** | 26.6 (3.06) | 81.67 (17.64) | <0.01 (HS) |
| **Hopelessness scale** | 5.3 (1.5) | 17.2 (2.0) | <0.01 (HS) |
| **Plasma IL-1β (pg/mL)** | 5.4 (1.57) | 26.67 (9.1) | <0.05 (S) |
| **Plasma IL-6 (pg/mL)** | 5.9 (0.96) | 23.47 (2.57) | <0.01 (HS) |
| **Plasma hsCRP (mg/L)** | 6.3 (1.07) | 38.7 (2.08) | <0.01 (HS) |

In the present study, there was a significant difference between patients with major depression and control group as regards BDI, HS, plasma IL-1β, IL-6 and hsCRP. There was no significant difference between the studied group and control cases as regards age, BMI, total cholesterol and HDL cholesterol.

**Table 2: Comparison between different grades of depression and plasma cytokines in Patient group.**

| | *BDI | | |
|---|---|---|---|
| | Mild (n=4) | Moderate (n=10) | Severe (n=6) |
| IL-1B | $^{a}$ 20.27 (0.64) | $^{b}$ 28.93 (2.53) | $^{b}$ 30.81 (3.5) |
| IL-6 | $^{a}$ 18.11 (2.4) | $^{b}$ 25.2 (1.4) | $^{b}$ 27.1 (2.0) |
| hsCRP | $^{a}$ 30.09 (1.3) | $^{b}$ 42.03 (2.25) | $^{b}$ 43.98 (2.7) |

*Different letters in each row mean significant difference

As shown in table 2; there was significant difference between patients scoring mild and those scoring moderate on BDI as regard mean scores of IL-1B, IL-6 and hsCRP. Also there was significant difference between patients scoring mild and those scoring severe on BDI as regard mean scores of IL-1B, IL-6 and hsCRP. There was no significant difference between patients scoring moderate and those scoring severe on BDI as regard mean scores of IL-1B, IL-6 and hsCRP.

**Table 3: Comparison between different grades of hopelessness and plasma cytokines in Patient group.**

| | *HS | | |
|---|---|---|---|
| | Mild (n=5) | Moderate (n=11) | Severe (n=4) |
| IL-1B | $^{a}$ 20.2 (1.6) | $^{b}$ 28.81 (1.9) | $^{b}$ 31.0 (2.9) |
| IL-6 | $^{a}$ 19.61 (1.8) | $^{b}$ 24.8 (0.95) | $^{b}$ 26.0 (2.69) |
| hsCRP | $^{a}$ 33.7 (1.7) | $^{b}$ 40.3 (2.78) | $^{b}$ 42.1 (3.1) |

*Different letters in each row mean significant difference

As shown in table 3; there was significant difference between patients scoring mild and those scoring moderate on HS as regard mean scores of IL-1B, IL-6 and hsCRP. Also there was significant difference between patients scoring mild and those scoring severe on HS as regard mean scores of IL-1B, IL-6 and hsCRP. There was non significant difference between patients scoring moderate and those scoring severe on HS as regard mean scores of IL-1B, IL-6 and hsCRP.

**Table 4: Comparison between past history of depression and plasma cytokines in Patient group.**

| | Positive (n=6) | Negative(n=14) | P-value |
|---|---|---|---|
| Mean BDI | 89.31 (2.9) | 74.03 (1.1) | <0.05 (S). |
| IL-1B | 27.4 (0.5) | 25.94 (1.6) | >0.05 (NS) |
| IL-6 | 23.7 (0.86) | 23.24 (2.25) | >0.05 (NS). |
| hsCRP | 39.97 (2.3) | 37.43 (1.7) | >0.05 (NS). |

As shown in table 4; there was significant difference between patients with positive past history of depression and those with negative past history of depression as regard mean scores of BDI. Also there was non significant difference between patients with positive past history of depression and those with negative past history of depression as regard mean scores of IL-1B, IL-6 and hsCRP.

**Correlation Study:**

**Table5: Correlation between Age, BMI, Cholesterol, HDL Cholesterol, BDI, HS, IL-1β, IL-6 and hsCRP in Patient group.**

| | Age | BMI | Cholesterol | HDL Cholesterol | BDI | HS | IL-1β | IL-6 | hsCRP |
|---|---|---|---|---|---|---|---|---|---|
| Age | ------ | r=0.23 (NS) | r=0.18 (NS) | r=0.42 (NS) | r=0.46 (S). | r=0.62 (S) | r=0.55 (S) | r=0.62 (S) | r=0.82 (S) |
| BMI | | ------ | r=0.59 (S) | r=0.76 (S) | r=0.12 (NS) | r=0.26 (NS) | r=0.18 (NS) | r=0.09 (NS) | r=0.19 (NS) |
| Cholesterol | | | ------ | r=0.72(S) | r=0.09 (NS) | r=0.34 (NS) | r=0.15 (NS) | r=0.18 (NS) | r=0.25 (NS) |
| HDL Cholesterol | | | | ------ | r=0.06 (NS) | r=0.28 (NS) | r=0.33 (NS) | r=0.04 (NS) | r=0.35 (NS) |
| BDI | | | | | ------ | r=0.49 (S) | r=0.56 (S) | r=0.47 (S) | r=0.75 (S) |
| HS | | | | | | ----- | r=0.65 (S) | r=0.82 (S) | r=0.92 (HS) |
| IL-1β | | | | | | | ----- | r=0.52 (S) | r=0.61 (S) |
| IL-6 | | | | | | | | ----- | r=0.50 (S) |
| hsCRP | | | | | | | | | ------ |

As shown in table 5; there was a significant correlation between mean scores of age and BDI, HS, IL-1β, IL-6 and hsCRP with non significant correlation between mean scores of age and BMI, Cholesterol and HDL Cholesterol. There was a significant correlation between mean scores of BMI and Cholesterol and HDL Cholesterol, with non significant correlation between mean scores of BMI and BDI, HS, IL-1β, IL-6 and hsCRP. There was also a significant correlation between mean scores of Cholesterol and HDL Cholesterol with non significant correlation between mean scores of Cholesterol and BDI, HS, IL-1β, IL-6 and hsCRP. There was also a non significant correlation between mean scores of HDL Cholesterol and BDI, HS, IL-1β, IL-6 and hsCRP. There was a significant correlation between mean scores of BDI and HS, IL-1β, IL-6 and hsCRP. There was also a significant correlation between mean scores of HS and IL-1β, IL-6 and hsCRP. There was a significant correlation between mean scores of IL-1β and IL-6 and hsCRP. There was also a significant correlation between mean scores IL-6 and hsCRP.

## Discussion

**Ross, (1999), McCaffery, (2006),** and **Yudkin, et al, (2000)** stated that ASCVD is fundamentally a chronic inflammatory disorder, consistent with his view, plasma cytokines has been shown to predict future risk of MI and to contribute to processes leading to ASCVD. In previous studies that examined the relation of plasma cytokines, and inflammatory mediators as a function of both severity of depressive symptoms and hopelessness, indicated a significant effect of hopelessness and severity of depressive symptoms on plasma cytokines, and inflammatory mediators levels. This interaction predicted plasma cytokines, and inflammatory mediators concentrations even after statistical adjustment for age, BMI, and lipids, factors associated with plasma cytokines, and inflammatory mediators. **Ridker, et al, (2000), McCarty, (1999), Chae , et al, (2001).**

Our study revealed a significant difference between patients with major depression and normal controls as regard mean scores of BDI, HS, plasma IL-6, IL-1B, and hsCRP.

These results (after exclusion of Age, BMI, and serum cholesterol as variables), might signifies the role of depression in altering levels of plasma cytokines and inflammatory markers.

Our results are matched with **Miller et al, (2002),** who observed a 40% increase in C-reactive protein and a 36% increase in interleukin-6 levels between depressive and non-depressive adults. Furthermore, similar results were observed in elderly individuals, **Kop, et al, (2002), Daniel and Thomas, (2004).** They also found a strong relation between depression and levels of C-reactive protein in both men and women. In particular, compared to non-depressive subjects, men with severe depression had 46% higher C-reactive protein levels.

They have been suggested that depression promotes systemic inflammation and increases plasma levels of inflammatory cytokines like IL-6, IL-1B, and acute-phase proteins like C-reactive protein, **Danner, et al, (2003), François, et al., (2004).**

On the contrary Steptoe, et al; found that, there were no associations between measures of depressive symptoms or hopelessness and markers of immune activation or inflammatory response. They concluded that factors such as the measures of depressive symptoms, the choice of inflammatory and immune indices, and sample size, are unlikely to be responsible for these null effects, **Steptoe, et al, (2003).**

Also, in our study we found that, patients with mild depression and hopelessness showed a significant difference with those with moderate and severe depression and hopelessness as regard mean scores of BDI, HS, plasma IL-6, IL-1B, and hsCRP. On the other hand there was a non significant difference between patients with moderate and severe depression on the same parameters.

These results might signify the role of severity of depressive symptoms in altering levels of plasma cytokines and inflammatory markers.

Our findings are in concordance with **Zorrilla, et al, (2001),** have suggested that IL-6 is significantly associated with major depressive disorder (MDD), even though negative findings have also been reported by **Reif, et al, (2001).** In contrast, **Lutgendorf, et al, (1999),** stated that there is a paucity of evidence for the relation of severity of depressive symptoms to IL-6. **Dentino, et al, (1999),** on the other hand have suggested that severity of depressive symptoms and depressed mood are positively associated with IL-6 in healthy, older adults.

**Sluzewska, et al, (1995),** concluded that, IL-6 is an important mediator of the acute-phase response, and higher levels of acute-phase proteins have been reported in depression. **Maes, et al, (1993),** found that hyperproduction of IL-6 and IL-1ß have been associated with the severity of depression; that is, higher serum levels have been found in patients with melancholic depression, **Maes, (1995).**

**Kent, et al, (1992) and Yirmiya, (1996),** stated that; cytokines may play a role in the pathophysiology of mood disorders. Of relevance to mood disorders, these cytokines can also induce "sickness behavior," which includes symptoms of fatigue, anorexia, anhedonia (loss of interest in usual activities), decreased psychomotor activity, and disappearance of body care activities. Smilarley, **Heinrich, et al, (1990)** found that; these signs and symptoms accompany the immunologic response to infection may overlap with the symptoms of major depression as a key regulator of the acute phase response.

Our study revealed a significant difference between patients with positive past history of major depression and those without past history of major depression as regard mean scores of BDI. However, such difference does not significantly affect plasma levels of IL-6, IL-1B, and hsCRP.

In our study the mean age was significantly correlated with the mean scores of plasma cytokines and inflammatory markers. These findings might signify the role of age in affecting mood state and plasma cytokines and inflammatory markers levels.

Our results are similar to **Ballou, et al, (1996)** and **Ershler, et al, (1993),** who found on their studies performed in a number of healthy volunteers found that circulating levels of IL-6, CRP, and other biomarkers of inflammation increase with age, although in those studies the definition of healthy status was questionable. **Wei, et al, (1992),** and **Miller, (2004)** founded the same results. On the contrary **Ahluwalia, et al, (2001),** in a previous study that screened participants with strict criteria for good health, adequate nutrition, and absence of diseases failed to detect any significant difference in the production of IL-1 and IL-6 between young, middle-aged, and older participants.

Our study revealed a significant correlation between mean scores of BDI, and HS, plasma IL-6, IL-1B, and hsCRP. Also a similar significant correlation between mean scores of HS, and plasma IL-6, IL-1B, and hsCRP.

These findings might highlights the relation between depressive symptoms and hoplessness on one hand and the plasma cytokines and inflammatory markers levels on the other hand.

Our findings are in concordance with **Rozanski, et al, (1999), and Marion et al (2003)** who found a significant positive correlation was found between cytokine production and acute-phase proteins, which suggests that activation of the inflammatory response system in depression is associated with increased production of the proinflammatory cytokines IL-1ß, IL-6, and INF-γ.

Also; **Lutgendorf, et al, (1999),** found that immune reaction as measured by proinflammatory cytokines is positively correlated with depressive symptoms and with the impaired feedback regulation of the HPA axis in major depression.

**Stoney and Engerbretson, (2000),** stated that hyperproduction of IL-6 and IL-1ß have been associated with the severity of depression; that is, higher serum levels have been found in patients with melancholic depression.

On the contrary **Anisman, et al, (1999),** concluded that IL -1ß was increased in patients with dysthymia and that cytokine alteration was associated with the chronicity of illness and the age at onset.

Results from the Physicians' Health Study indicated that increasing levels of plasma IL-6 and IL-1B are associated with an increasing number of traditional risk factors (e.g., hypertension, hyperlipidemia, smoking), **Ridker, et al, (2000).** The current findings are the first to demonstrate that higher plasma IL-6 and IL-1B levels are also associated with the presence of both hopelessness and severity of depressive symptoms. That plasma IL-6 predicts future risk of cardiovascular events, as well as all-cause mortality, leads to the possibility that men who are both hopeless and exhibit depressive symptoms, even in the mild to moderate range, are at heightened risk for all-cause mortality and cardiac events**, Yudkin, et al, (2000), Gershenfeld, (2005).**

Consistent with this speculation, one study has reported greater all-cause mortality among hopeless individuals with depressive symptoms, **Barefoot, et al, (1995).** With this one exception, no other study has examined the combined effect of hopelessness and severity of depressive symptoms on health outcomes or cardiovascular end points. The current observations, therefore, add relevance to the argument for examining the joint effect of hopelessness and severity of depression in predicting outcome measures in epidemiological studies of cardiovascular disease as well as laboratory studies of biological risk factors.

The current study did not address possible mechanisms that could explain these observations. However, inclusion criteria (e.g., healthy, free of any acute medical conditions, nonsmokers, no medications whether prescribed or over-the counter) and statistical controls (e.g., age, BMI, lipids) implemented in this study support the conclusion that higher plasma IL-6 IL-1B, and hsCRP levels among hopeless men with mild to moderate symptoms of depression are not mediated by these factors. Thus, elevated IL-6 IL-1B, and hsCRP levels in hopeless men with depressive symptoms may be due, in part, to other factors, possibly stress-related in nature, **Steptoe, et al, (2001), Paik, et al, (2000), O'BRIEN, (2006).**

## Conclusion

The current study demonstrates the effect of hopelessness and severity of depressive symptoms on the plasma concentration of IL-6 IL-1B, and hsCRP in apparently healthy men. This observation was independent of the effects of traditional risk factors of cardiovascular disease that are known to influence plasma IL-6 IL-1B, and hsCRP, such as age, smoking, BMI, blood pressure, and lipids. The current findings raise the possibility that, among hopeless men with depressive symptoms, plasma IL-6 IL-1B, and hsCRP is either a marker for future risk of ASCVD or is a pathophysiological mechanism leading to increased risk of ASCVD. Whatever the case may be, the current findings broaden our understanding of how hopelessness in conjunction with depressive symptoms may impact cardiovascular disease risk via elevations in plasma IL-6 IL-1B, and hsCRP. It remains to be seen whether these observations can be replicated in women and whether this relationship can be moderated by prophylactic interventions that include lifestyle changes and/or anti-inflammatory therapies, both known to reduce the risk of cardiovascular disease.

## Recommendation

To study the effect of depression and hopelessness on a large number of patients for better demonstration of the link between depression and CVD. To include female patients in future studies where females are known to suffer depression more than males. To study the effect of other psychiatric disorders such as anxiety disorders on plasma cytokines and inflammatory mediators. To screen cardiac patients for depressive disorders that might be considered alone as a risk factor for their medical condition.

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# Weight Reduction, Physical Activity and psychotherapeutic intervention in Chronic Hepatitis C Patients: Impact on Liver Functions and Quality of Life.

***Mohammad Ezat Amin, Abdel Bar M. y and Zahra A.***

## Abstract

The effect of significant weight loss and the role of psychotherapeutic intervention on chronic liver disease remain unclear.

The aim of this study was to investigate the effect of weight loss and psychological support on obese chronic HCV patients as regards biochemical studies and various psychological domains. Forty four obese chronic HCV patients were included in our study, and were divided into two groups. Group A (nighnteen patients) completed a 3 month diet control and exercise regimen; liver function tests, serum insulin & blood glucose levels and weekly psycho-therapeutic intervention and psychological assessment using HRQL,HAD,BIQ and SERS were performed before the start and after three months of life style intervention program. Group B (twenty five patients); control.

On completion of the intervention, 16 patients (66.7%) had achieved weight loss with a mean reduction of BMI of 5.2 (kg/m$^2$). Improvements in serum alanine aminotransferase (ALT) levels were correlated with the amount of weight loss ($p=<0.05$ (S)). Improvements in fasting serum insulin levels were also correlated with weight loss ($p=<0.05$ (S)). Quality of life, depression, anxiety, self-esteem, and satisfaction with body image was significantly improved after weight loss. In summary, we have demonstrated major improvement in the biochemical studies and psychological aspects in overweight patients with liver disease after weight loss and psycho-therapeutic intervention.

## Introduction

The prevalence of obesity and overweight has risen at an alarming rate over the past 20 years **(Mokdad, et al, 2003, Marchesini, et al, 2001)**. There is a development of significant public health concern in light of the numerous and often interconnected health consequences of these conditions, including type 2 diabetes, hypertension, dyslipidemia, and heart disease. Recently, a novel hepatic sequela of obesity has been described: nonalcholic fatty liver disease (NAFLD) **(Mulhall, et al, 2002, Angulo and Lindor, 2002)** which is defined as "significant lipid deposition in the hepatocytes of the liver parenchyma in a patient without a history of excessive alcohol ingestion" **(Mulhall, et al, 2002)**. Most individuals with NAFLD in its uncomplicated form (simple steatosis) are asymptomatic. However, a subset progresses to more severe manifestations of the NAFLD disease spectrum, including nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and liver failure **(Mulhall, et al, 2002, Angulo and Lindor, 2002, Nakao, et al, 2002).**

Obesity is also recognized as an independent risk factor for the progression of fibrosis in other chronic liver diseases **(Clouston and Powell, 2002).** A number of studies have now demonstrated an association between increased BMI or visceral adiposity and hepatic steatosis and fibrosis in patients infected with hepatitis C virus (HCV) **(Adinolfi**, **et al, 2001**, **Hourigan, et al, 1999)**. In overweight patients with chronic HCV, studies recently demonstrated an association between increasing insulin levels and increasing hepatic fibrosis, suggesting that host metabolic factors also contribute to disease progression **(Hickman, et al, 2003, Raynard**, **et al, 2002).**

The role of increased BMI and steatosis as co-morbid factors in the progression of fibrosis has important therapeutic implications. Although gradual weight reduction is recommended as a first step in the management of patients with obesity related fatty liver, there is a paucity of long term outcome data on the effect of modest weight loss on liver disease or associated metabolic factors. Modest weight loss in these patients was associated with an improvement in elevated liver enzymes due to a reduction in steatosis, and in some patients, an improvement in necroinflammatory activity and fibrosis **(Hickman, et al, 2002).**

A number of studies have consistently reported impairment in health related quality of life (HRQL) in patients with chronic liver disease compared with healthy individuals **(Bonkovsky and Woolley, 1999**, **Foster, et al, 1998).** In addition, there is a dose-response relationship between BMI and the degree of HRQL impairment **(Ware, et al, 1999, Hussain, et al, 2001).** It remains unknown whether the beneficial effects of weight reduction on HRQL are observed in patients with chronic liver disease and are sustainable long term **(Fontaine and Barofsky, 2001)**. Patients with liver cirrhosis and depression had a significantly poorer perceived quality of life and poorer adaptive coping compared with nondepressed patients. A significantly higher number of patients with depression had a viral hepatitis (B/C)-associated cirrhosis compared with patients without depression **(Singh, et al, 1997, Elizabeth, et al., 2004, Schaefer, et al., 2005).**

Implications for medical care in CHC are evident; addressing psychosocial factors may have positive results on the outcome of patients with hepatitis C by improving compliance and reducing risk behavior **(Lee, et al, 1997, Clementine, et al., 2004).** Quality of life for the obese person is diminished in countless ways. Frequently the obese person struggles with depression, hopelessness, and despair **(Hulya, et al, 1997, Kraus, et al., 2005).**

The aim of this study was to investigate the effect of lifestyle intervention involving weight loss, increased physical activity and psychological support on liver biochemistry, fasting insulin levels, and various psychological domains in overweight HCV patients.

## Patients & Methods

Fourty four obese chronic HCV patients were seen in the liver clinic at Kasr El-Ainy Hospital between 2005 and 2006. They were invited to participate in the study. Informed consent was obtained from each patient. Criteria for entry into the study were overweight or obese (BMI $\geq$ 25 kg/m$^2$), non-HBV educated patients capable of obeying instructions, no current major psychiatric disorder (using the DSM-IV Axis I disorders–criteria, **Ventura, et al, 1998**), or current intake of psychotropic medications which might affect the body weight. All patients included in the study were unable to afford, or non-responders to, current antiviral treatment **(Matteoni, et al, 1999)**.

### Modulation of Lifestyle

Lifestyle intervention included a three month weight reduction period. During this period, patients were seen on a weekly basis. A thirty minutes Weekly psycho-therapeutic intervention (ventilative, supportive, educational and cognitive behavioral), weight and waist circumference measurements, exercise (walking for one hour daily) and diet were revised with each patient at each visit **Hickman, et al, (2002), Hill, et al, (1999).**

### Biochemical and metabolic studies

After overnight fasting, 10 ml of blood were collected from anticubital vein by venipuncture at months 0, 3. Blood samples were collected in two types of clean glass test tubes. The first group of test tubes contained fluoride for enzymatic determination of fasting plasma glucose, using a SENTINEL CH. commercially available kit **(Trinder, 1969).** The second groups of test tubes were incubated at 37°c for 20 minutes then were centrifuged at 3000 rpm to separate serum. Serum samples were divided into several aliquots for measurements of insulin, ALT, total cholesterol and triacylglycerols. Serum insulin was measured by an enzyme-linked immunosorbent assay (ELISA) kit commercially available from the DRG International, Inc. USA using Mrx dynatech laboratories ELISA reader **(Delmas, 1986).** Serum ALT was measured kinetically using SENTINEL CH. commercially available kit **(IFCC, 1980).** Serum total cholesterol **(Trinder, 1969);** and triacylglycerols **(Mc Gowan, et al, 1983),** were measured enzymaticaly using SENTINEL CH. commercially available kit. HCV antibodies, HBsAg, HBc total were done for all patients at the start of the study.

### Health related quality of life (HRQL)

HRQL was measured at 0 and 3 months using the short form 36 (SF-36) questionnaire. The SF-36 questionnaire measured eight multi-item scales called health domains **(Ware and Sherbourne, 1992)**. Two summary scores, the mental component score (MCS) and the physical component score (PCS), were calculated via a weighted combination of the eight health domains **(Clark and Fallowfield, 1986, Australian Bureau of Statistics, 1995)**.

### Hospital Anxiety and Depression Scale (HADS):

The HADS consists of seven items for anxiety (HADS-A) and seven for depression (HADS-D). The items are scored on a four-point scale from zero (not present) to three (considerable). The item scores are added, giving sub-scale scores on the HADS-A and the HADS-D from zero to 21 **(Zigmond and Snaith, 1983, Bjelland, et al, 2001, Herrmann, 1997).**

### Body Image Questionnaire (BIQ):

The questionnaire gives a general assessment of body image. More important than absolute score, is the relative shift in score toward an overall more positive relationship between self and body. The questionnaire consists of 12 statements. For each of the statements, the patient rates the degree to which it applies to him from 0 to 3. In general, the final score may suggest the following: 0 - 7 Great attitudes / Keep it up. 8-14 slightly dissatisfied. 15-21 moderately dissatisfied. 22-28 Very dissatisfied. 29-36 extremely dissatisfied **(Licvoli and Brannon, 1998).**

**Rosenberg's Self- esteem Scale (RSE):** Respondents are asked to strongly agree, agree, disagree, or strongly disagree with the scale-items. The 10 items will be combined with 20 items that have been compiled and based on already existing tests and scales relating to the variable of self-esteem. These tests and scales include the Self-Esteem Rating Scale (SERS) and the Index of Self-Esteem (ISE). Subjects will be told that all items must be answered and assigning it a value of 1, 2, 3, or 4 with 1 corresponding to a response that shows the lowest self-esteem. So, a response of "SA" or "SD" will either be assigned 1 or 4; a response of "A" or "D" will be assigned either 2 or 3 **(Rosenberg, 1965)**.

### Statistical analysis

Continuous normally distributed variables were summarized as mean ± standard deviation (SD). They were compared by paired and unpaired t-student test when appropriate. The degree of association between ordinal variables was assessed using Spearman correlation coefficient (*r*). Categorical data were compared using a $\chi^2$ test.

All analyses were carried out using SPSS software version 10.0 (SPSS Inc. Chicago, Illinois, USA). Statistical significance was taken at a level of 5%.

## Results

### Study patients

Ten patients out of the included cases did not complete the study. Demographic information for the 34 chronic obese HCV patients (Group A, n = 16; Group B, n =18) is summarized in table 1. Three patients (Group A, n= 1; Group B, n = 2) had type 2 diabetes according to defined criteria **(WHO, 1999)**.

**Table 1: Demographic and biochemical parameters of patients in group A and group B prior to enrollment in life style intervention program.**

| **Parameter** | **Group A (n = 16)** | **Group B (n = 18)** | **p Value*** | **Reference range** |
|---|---|---|---|---|
| **Age (y)** | 46.4 (2.08) | 47.4 (1.1) | >0.05 (NS) | |
| **Sex M/F** | 9/7 | 10/8 | >0.05 (NS) | |
| **Type 2 DM (n)** | 1 | 2 | >0.05 (NS) | |
| **BMI (kg/m$^2$)** | 33.8 (1.4) | 35.2 (2.2) | >0.05 (NS) | |
| **Waist (cm)** | 118.3 (13.1) | 124.2 (3.5) | >0.05 (NS) | |
| **ALT (U/l)** | 128.7 (7.6) | 120.1 (2.1) | >0.05 (NS) | <35 U/l |
| **Cholesterol (mg/dL)** | 226.5 (21.5) | 231.3 (7.3) | >0.05 (NS) | <240 mg/dL |
| **Triglyceride (mg/dL)** | 130.2 (16.4) | 137.2 (6.6) | >0.05 (NS) | <150 mg/dL |
| **Insulin (mU/l)** | 14.0 (2.6) | 15.7 (2.1) | >0.05 (NS) | <20 mU/l |
| **Glucose (mg/dL)** | 106.8 (1.4) | 108.5 (7.9) | >0.05 (NS) | <120 mg/dL |

**Table 2: Demographic and biochemical parameters of patients in group A and group B after 3 months of enrollment in life style intervention program**

| **Parameter** | **Group A (n = 16)** | **Group B (n = 18)** | **p Value*** | **Reference range** |
|---|---|---|---|---|
| **BMI (kg/m$^2$)** | 28.6 (0.6) | 35.0 (6.7) | <0.05 (S) | |
| **Waist (cm)** | 109.6 (2.6) | 125.1 (0.79) | <0.05 (S) | |
| **ALT (U/l)** | 88.1 (2.5) | 117.7 (15.6) | <0.05 (S) | <35 U/l |
| **Cholesterol (mg/dL)** | 193.3 (11.5) | 227.3 (9.5) | <0.05 (S) | <240 mg/dL |
| **Triglyceride (mg/dL)** | 113.7 (11.9) | 136.7 (6.1) | <0.05 (S) | <150 mg/dL |
| **Insulin (mU/l)** | 10.2 (0.75) | 15.4 (2.9) | <0.05 (S) | <20 mU/l |
| **Glucose (mg/dL)** | 94.3 (5.0) | 113.3 (4.2) | <0.05 (S) | <120 mg/dL |

**Table 3: Demographic and biochemical parameters of patients in group A before and after 3 months of enrollment in life style intervention program**

| **Parameter** | **Before** | **After** | **p Value*** | **Reference range** |
|---|---|---|---|---|
| **BMI (kg/m$^2$)** | 33.8 (1.4) | 28.6 (0.6) | <0.05 (S) | |
| **Waist (cm)** | 118.3 (13.1) | 109.6 (2.6) | <0.05 (S) | |
| **ALT (U/l)** | 128.7 (7.6) | 88.1 (2.5) | <0.05 (S) | <35 U/l |
| **Cholesterol (mg/dL)** | 226.5 (21.5) | 193.3 (11.5) | <0.05 (S) | <240 mg/dL |
| **Triglyceride (mg/dL)** | 130.2 (16.4) | 113.7 (11.9) | <0.05 (S) | <150 mg/dL |
| **Insulin (mU/l)** | 14.0 (2.6) | 10.2 (0.75) | <0.05 (S) | <20 mU/l |
| **Glucose (mg/dL)** | 106.8 (1.4) | 94.3 (5.0) | <0.05 (S) | <120 mg/dL |

**Table 4: Demographic and biochemical parameters of patients in group B before and after 3 months**

| **Parameter** | **Before** | **After** | **p Value*** | **Reference range** |
|---|---|---|---|---|
| **BMI (kg/m$^2$)** | 35.2 (2.2) | 35.0 (6.7) | >0.05 (NS) | |
| **Waist (cm)** | 124.2 (3.5) | 125.1 (0.79) | >0.05 (NS) | |
| **ALT (U/l)** | 120.1 (2.1) | 117.7 (15.6) | >0.05 (NS) | <35 U/l |
| **Cholesterol (mg/dL)** | 231.3 (7.3) | 227.3 (9.5) | >0.05 (NS) | <240 mg/dL |
| **Triglyceride (mg/dL)** | 137.2 (6.6) | 136.7 (6.1) | >0.05 (NS) | <150 mg/dL |
| **Insulin (mU/l)** | 15.7 (2.1) | 15.4 (2.9) | >0.05 (NS) | <20 mU/l |
| **Glucose (mg/dL)** | 108.5 (7.9) | 113.3 (4.2) | >0.05 (NS) | <120 mg/dL |

At the start of the present study, there was no significant difference between both groups as regards the demographic and biochemical parameters of patients.

After 3 months there was a mean decrease of BMI of 5.2 (kg/m$^2$) and a mean decrease in waist circumference of 8.7 cm in group A. In group B there was no significant difference in weight and waist change.

Serum ALT levels improved significantly with weight reduction ($p < 0.05$) in group A. There was a mean reduction in ALT of 31.2% (p = 0.02) while group B showed no significant change.

In addition to decreasing serum ALT levels, weight reduction significantly decreased cholesterol of 14.6% (p <0.05), triacylglycerol of 12.7% (p< 0.05) and fasting insulin levels of 27.1% (<0.05) while in group B there was no significant change.

**Psychological assessment**

**Table 5: Mean scores of HRQL of patients in group A and group B before and after 3 months.**

| | **Health related quality of life (HRQL)** | | | |
|---|---|---|---|---|
| | **Group A** | | **Group B** | |
| | **PCS** | **MCS** | **PCS** | **MCS** |
| **Before** | 40.3 (4.9) | 36.1 (1.6) | 38.1 (3.1) | 35.4 (1.0) |
| **After 3 months** | 54.7 (4.5) | 51.6 (2.5) | 37.7 (2.1) | 38.7 (2.3) |
| ***P- Value** | <0.05 (S) | <0.05 (S) | >0.05 (NS) | >0.05 (NS). |

*P value of the difference before and after life style intervention in the same group

As shown in table 5 and table 5A; there was a significant difference between mean scores of PCS and MCS in group A patients before intervention and after 3 months. There was also a significant difference between mean scores of PCS and MCS in group A patients and group B patients after 3 months. There was no significant difference between mean scores of PCS and MCS in group A patients and group B patients before intervention.

There was no significant difference between mean scores of PCS and MCS in group B patients before intervention and after 3 months.

**Table 6: Mean scores of HAD Scale of patients in group A and group B before and after 3 months.**

| **Hospital Anxiety and Depression Scale(HAD)** | | | | | | |
|---|---|---|---|---|---|---|
| | **Depression** | | | **Anxiety** | | |
| | **Group A** | **Group B** | **P-Value** | **Group A** | **Group B** | **P-Value** |
| **Before** | 14.8 (0.67) | 13.6 (1.29) | >0.05 (NS) | 15.7 (1.2) | 15.1 (1.18) | >0.05 (NS) |
| **After 3 months** | 10.3 (0.5) | 14.1 (1.6) | <0.05 (S) | 10.5 (0.4) | 14.2(1.04) | <0.05 (S) |
| **P value** | <0.01 (HS) | >0.05 (NS) | | <0.01 (HS) | >0.05 (NS) | |

As shown in table 6; there was a significant difference between mean scores of depression and anxiety in group A patients before intervention and after 3 months. There was also a significant difference between mean scores of depression and anxiety in group A patients and group B patients after 3 months. There was no significant difference between mean scores of depression and anxiety in group A patients and group B patients before intervention. There was no significant difference between mean scores of depression and anxiety in group B patients before intervention and after 3 months.

**Table 7: Mean scores of Body Image Questionnaire and Rating Scale for Self-esteem of patients in group A and group B before and after 3 months.**

| | Body Image Questionnaire(BIQ) | | | Self-esteem Rating Scale(SERS) | | |
|---|---|---|---|---|---|---|
| | **Group A** | **Group B** | **P-Value** | **Group A** | **Group B** | **P-Value** |
| **Before** | 26.3 (1.55) | 25.6 (2.0) | >0.05 (NS) | 46.9 (1.35) | 48.6 (4.9) | >0.05 (NS) |
| **After 3 months** | 18.1 (2.0) | 26.3 (0.76) | <0.05 (S) | 64.5 (0.58) | 50.3 (1.6) | <0.05 (S) |
| **P-Value** | <0.05 (S) | >0.05 (NS) | | <0.01 (HS) | >0.05 (NS) | |

As shown in table 7; there was a significant difference between mean scores of BIQ and SERS in group A patients before intervention and after 3 months. There was also a significant difference between mean scores of BIQ and SERS in group A patients and group B patients after 3 months. There was no significant difference between mean scores of BIQ and SERS in group A patients and group B patients before intervention.

There was no significant difference between mean scores of BIQ and SERS in group B patients before intervention and after 3 months.

**Table 8: Comparison between female and male patients in group A as regard Depression, Anxiety, PCS, MCS, BIQ and SERS before start of program.**

| | **Female** | **Male** | **P-value** |
|---|---|---|---|
| **Depression** | 16.2 (0.65) | 13.4 (0.62) | <0.01 (HS) |
| **Anxiety** | 16.8 (0.74) | 14.6 (1.19) | <0.05 (S) |
| **PCS** | 37.9 (0.32) | 42.7 (2.35) | <0.05 (S) |
| **MCS** | 34.6 (1.69) | 37.7 (0.36) | <0.05 (S) |
| **BIQ** | 29.2 (0.49) | 23.2 (1.17) | <0.01 (HS) |
| **SERS** | 42.3 (1.18) | 51.5 (1.15) | <0.01 (HS) |

As shown in table 8; there was a significant difference between mean scores of depression, anxiety, PCS, MCS, BIQ and SERS in female and male patients in group A patients before intervention.

**Correlative Study:**

**Table 9: Correlation coefficients of Age, BMI, Waist, PCS, MCS, BIQ, Dep., Anx. and SERS in group A patients before treatment.**

| | **Age** | **BMI** | **Waist** | **PCS** | **MCS** | **BIQ** | **Dep.** | **Anx.** | **SERS** |
|---|---|---|---|---|---|---|---|---|---|
| **Age** | ------- | 0.52 | 0.49. | 0.16. | 0.43 | 0.17 | 0.47 | 0.08 | 0.23 |
| **BMI** | | ------- | 0.89* | -0.65* | -0.72* | 0.59* | 0.82* | 0.63* | -0.61* |

* Significant correlation at the level of 0.05

As shown in table 9 our study revealed (in group A) a significant positive correlation between mean score of BMI and BIQ, HAD Depression and HAD Anxiety Scales. On the other hand there was a significant inverse correlation between mean score of BMI and SERS, PCS and MCS Scales.

PCS and MCS Scales mean score shows a significant inverse correlation ($P<0.05$) with mean scores of BIQ, HAD Depression and HAD Anxiety Scales ($r=-0.76$, -0.69, -0.59 and -0.52, -0.64, -0.84 respectively). There was also a significant positive correlation between mean scores of PCS and MCS Scales and SERS ($r=0.70$, 0.66 respectively, $P<0.05$).

BIQ mean score shows a significant positive correlation with mean scores of HAD Depression and HAD Anxiety Scales ($r=0.52$ and 0.59 respectively, $P<0.05$). There was also a significant negative correlation between BIQ mean score and SERS ($r=-0.64$, $P<0.05$).

HAD Depression and HAD Anxiety Scales mean scores shows a significant negative correlation with mean scores of SERS ($r=-0.69$ and -0.74 respectively, $P<0.05$).

PCS mean score shows a significant positive correlation with mean score of MCS($r=0.86$, $P<0.01$), whereas HAD Depression Scale mean score shows a significant positive correlation with mean score of HAD Anxiety Scales mean score ($r=0.84$, $P<0.01$).

There was no significant correlation between the mean age of patients and BMI, Waist Circumference, PCS, MCS Scales, HAD Depression, HAD Anxiety Scales, BIQ and SERS mean scores.

## Discussion

Our results demonstrate that weight reduction, psychotherapeutic intervention and increased physical activity result in a sustained improvement in ALT, fasting insulin levels, HRQL, HAD, BIQ, and SERS in overweight HCV patients.

Previous studies demonstrated that weight loss reduced hepatic steatosis and fibrosis in patients with chronic HCV **(Hickman, et al, 2002).** In our study; although liver biopsies were not performed, it is likely that the improvement in ALT and fasting insulin in patients who had weight loss was accompanied by a reduction in hepatic steatosis and necroinflammatory activity. With long term weight maintenance there is likely to be an even greater resolution of hepatic fibrosis.

Overall, in our patient cohort, the decrease in ALT and insulin levels was associated with the amount of weight loss. However, an improvement in ALT and insulin levels was seen with a weight loss of as little as 4–5% body weight without necessarily normalizing BMI. These findings are in accordance with results of recent type 2 diabetes intervention studies where the average amount of weight loss was not large yet resulted in a substantial reduction in the incidence of diabetes **(Tuomilehto, et al, 2001, Pan, et al, 1997, Knowler, et al, 2002).** Waist circumference remained significantly below enrolment measurements in all patients, regardless of weight change during follow up **(Rothacker and Blackburn, 2000, Schwartz, et al, 1995).**

Our study was not designed to test the relative contribution of dietary changes, weight loss, or increased physical activity to the improvement in liver enzymes and insulin levels, and the individual effects of these components warrant further study.

It is widely accepted that exercise has an important role in the treatment of visceral adiposity and insulin resistance. Our data further support the important role of exercise in the successful maintenance of weight loss in patients with chronic liver disease **(Rosenberg, 1965, Hoag, 1995).**

The success of weight maintenance in our study was probably due to the initial intensive programme combined with psychotherapeutic intervention and long term follow up. Increasing the length and frequency of standard dietetic intervention improves long term success **(Perri, et al, 1989).** In addition to the substantial cost of chronic liver disease to the health care system, the reduced HRQL in our patients illustrates the significant personal and social burden on those afflicted. Comorbid conditions such as obesity significantly contribute to the reduced feeling of well being in these patients, irrespective of disease severity.

Our study revealed higher levels of depression, anxiety and body image disturbance, and lower levels of QOL and self esteem at the start of study in both groups. This might reflect the degree of psychological suffering of HCV patients. These findings are correlated with those of **(Lee, et al 1997** and **Michael, 2006)** who stated that a high percentage of patients with hepatitis C showed clinically relevant scores for depression and anxiety. Also **Perry, et al, (1993)** and **Martin, et al., (2003)** found that depression, unrelated to IFN therapy, was the most common associated disorder in CHC. **Herrmann, (1997)** stated that the mean score of anxiety was higher or equal in patients with CHC compared with cancer patients.

**Foster, et al, (1998)** and **Cinda, et al., (2002**) showed that the reduction in quality of life scores in HCV patients could not be attributed to the degree of liver inflammation or the mode of acquisition of the infection; they suggested that the time of "knowledge" about hepatitis C infection seems to be one of the main variables influencing the emotional state.

The significant positive correlation between mean score of BMI and BIQ, HAD Depression and HAD Anxiety Scales; in addition to the significant negative correlation between mean score of BMI and SERS, PCS and MCS Scales might indicate that obesity represents a psychological burden to HCV patients which lead to worsening of mood states, disturb body image, lower self-esteem and also affect QOL.

Our findings are appropriate with **Blues, (2004)** who found that Obesity carries a large social stigma and may bring on depression if it negatively affects self-esteem, body image or social mobility. It may even disrupt the normal hormonal pathways. He also concluded that depression may also bring on obesity, if a person lacks the energy to exercise or is immobilized by stress.

**Hulya, et al (1997)** found that sociodemographic, psychosocial, and genetic factors may render certain obese individuals more prone to depression or vice versa. Physiological and behavioral variables that link obesity and depression have received are evident. Also **Mruk, (1996)** stated that Quality of life for the obese person is diminished in countless ways. Frequently the obese person struggles with depression, hopelessness, and despair.

**Goldsmith, et al, (1992), Cash, (1993) and Fitzgibbon, et al (1993)** found that individuals seeking treatment for weight loss have consistently demonstrated a higher prevalence of distress than their nontreatment-seeking counterparts. They also found that obese treatment seekers show elevated levels of depression, binge eating, general psychiatric symptoms, and body-image distress. **Goldsmith et al, (1992)** reported that 55.6% of their participants who were seeking weight-loss treatment met criteria for current or past psychiatric illness, especially major depression and dysthymia.

The significant improvement in mood state, satisfaction with body image, self-esteem and QOL in our HCV patients in group A; following the physical and psychological intervention might highlights the role of psychotherapeutic intervention in alleviating psychological suffering of patients. The psychotherapy sessions might have a role in improving depressive and anxiety symptoms, elevation of self-esteem, satisfaction with body and QOL through cognitive and behavioral techniques that aimed at correcting maladaptive cognitive schemata and automatic thoughts; in addition to behavioral tasks which aimed at challenging maladaptive behaviors and acquiring healthy behaviors.

Of relevance at start of our study female patients showed higher levels of depression, anxiety, dissatisfaction with their bodies, and lower self-esteem and QOL than male patients in both groups. This might be on one hand due to the higher incidence of depression and anxiety in females in general population. On the other hand these differences might be due to the higher impact of obesity and physical suffering (HCV) on females in our culture. On the other there was non significant difference between female and male patients in group A after intervention which might reflect a higher benefit of females throughout the program than males in the same group. This might be due to the higher need for support in female patients which was met with in psychotherapy sessions. These findings are correlated with **Sarwer, et al, (1998)** and **Evangelia, et al, (2006)** who found that obese women have stronger relationship between body-image dissatisfaction and depression and self-esteem.

Finally; in our study we found that the rate of drop out of HCV patients was higher in group B (7) than in group A patients (3). This might be due to the better physical and psychological care given to group A patients; also the frequent and close follow up might have a role. This finding is in agreement with **Lee, et al (1997)** who found that psychosocial factors may have positive results on the outcome of patients with hepatitis C by improving compliance and reducing risk behavior.

This study demonstrates that investment in weight reduction and psychological support has the ability to reduce risk factors associated with progression of liver disease, decrease abnormal liver enzymes, and improve quality of life. Importantly, these changes were achievable and sustainable with relatively small but persistent changes in lifestyle. These results suggest that treatment of overweight patients and psychological support should form an important component of management of those with chronic liver disease.

## Conclusions:

HCV patients suffer a multitude of physical and emotional system.

Obesity represents a major problem to HCV patients.

Weight reduction program and physical activity improves not only weight but also liver function.

Psychotherapeutic intervention alleviates an important part of HCV patients' suffering & improves QOL of such patients. Also it elevates self-esteem and satisfaction with body image.

**Recommendations:**

Addressing psychological care as an essential part of managing including physical activities and modulation of lifestyle is to be implemented to HCV patients.

A survey study including a larger number of HCV patients is recommended to speculate the prevalence of psychiatric disorders and psychiatric symptoms of these patients.

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**Abbreviations:** HCV, hepatitis C virus; BMI, body mass index; ALT, alanine aminotransferase; HRQL, health related quality of life; SF36, short form 36; PCS, physical component score; MCS, mental component score; HADS, Hospital Anxiety and Depression Scale; BIQ, Body Image Questionnaire; SERS Self-Esteem Rating Scale and RSE Rosenberg's Self- esteem Scale.

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# Parenting Stress Index among Mothers of Conduct Disorder Children

***Sayed M, Hussein H, El-Batrawy A, Zaki N and El Gaafary M***

## Abstract:

The objective is to study the parenting stress among mothers of children with conduct disorder and to highlight the possible risk factors attributed to the co-occurring stress. A case control study was conducted on 30 mothers of conduct children and a matched control group. Both groups underwent the following: semi-structured clinical interview and parenting stress index. Conduct children were diagnosed according to the ICD-10 and underwent the following: semi-structured clinical interview and a revised-behavior problem checklist. Mothers of conduct children experienced a significantly higher parenting stress score than the control and international scores, including total, parent and child domains scores. The maternal distress is experienced in all dimensions of the parent's functioning including parent's sense of competence, restriction of role, social isolation, and parental attachment relationship with spouse, parental health and parent depression and the distress is also predicted by the presence of inattention, hyperactivity, psychotic behavior, anxiety withdrawal, duration of the illness, delay to start treatment, age of the child and mother's education.

## Introduction:

Conduct disorder (CD), as defined in the DSM-IV, is characterized by a pervasive and persistent pattern of aggressive, deceptive and destructive behavior that usually begins in childhood or adolescence. CD symptoms are the primary presenting problems for psychiatric referral among children and adolescents in the US, and youth diagnosed with CD report higher levels of distress and impairment in almost all domains of living compared with youth with other mental disorders. Moreover, prior prospective studies have shown that conduct problems during childhood or adolescence are associated with significantly increased risk of other mental disorders, legal problems, and premature mortality ***(Nock et al. 2006).***

Several prior studies have used DSM-IV criteria to evaluate the prevalence of CD in other countries or in selective samples within the US, but these data are of limited use in estimating the prevalence of CD in the general US population. Based on these prior studies, the lifetime prevalence of CD has been estimated at between 6% and 16% for males and 2% and 9% for females in the US. However, in addition to limitations in the sampling procedures used, these estimates are based on DSM-III and DSM-III-R criteria. Given that even minor changes in the diagnostic criteria of CD have been shown to result in major differences in prevalence, these estimates are unlikely to represent the prevalence of DSM-IV CD accurately ***(Maughan et al. 2004).***

Examination of the collaboration of personal, family, components provides information on the complex of CD as well as an avenue for providing interventions. Personal characteristics and features, such as irritability, aggressiveness, and cognitive difficulties, are crucial for identifying markers for the onset of antisocial behavior. The perpetuation of these characteristics is mitigated by experiences with parents. Each of these components can intensify or minimize the extent to which antisocial behaviors are developed. Parent and family effects can range from familial stress to member criminality or psychopathology to discipline practices. Additionally, the quality of parent-child interactions can create, inadvertently encourage, or negate antisocial behavior. This is often a common area of change employed in interventions and a primary area of prevention ***(Jimerson et al.2002).***

ADHD when becomes comorbid with conduct disorder in children is commonly associated with disturbances in family and marital functioning, disrupted parent-child relationships and increased level of parenting stress and parental psychopathology ***(Johnston and March, 2001).***

Researchers studying the impact of raising a child with disruptive behavior on parents have emphasized that increased caretaking demands exist for parents throughout childhood and adolescence that could have adverse impact on parents with increased parenting related stress that they will experience. Some of these studies were done on parents of ADHD children showing more parenting related stress than other parents ***(Biederman, 2003).***

A study compared the levels of perceived stress on several dimensions of parenting in mothers and fathers of conduct disorder, autistic, Down syndrome, and normal children. Results showed that mothers and fathers report very similar levels of stress when parenting exceptional children, although their patterns of stress change as a function of the child's difficulties. Parents of conduct disorder children are most stressed, closely followed by parents of autistic children, while parents of Down syndrome children closely resemble and, in some respects, appear less stressed than parents of normal children ***(Noh et al. 1989).***

The aim of this work is to study the parenting stress among mothers of Conduct disorder children, to highlight the possible risk factors attributed to the co-occurring stress.

**Subjects and methods:**

This case control study was done on 15 mothers of conduct disorder children who were diagnosed according to the ICD-10 diagnostic criteria. They were recruited from the Child Psychiatry Clinic, Institute of Psychiatry, Ain Shams University. The control group is the hospital workers mothers of healthy children matched for age, sex, and socioeconomic status with mother of conduct disorder children.

**Both Conduct disordered children and healthy children were subjected to the following:**

**1) Semi-structured psychiatric interview according to ICD-10:**

The patients were interviewed guided by a psychiatric history-taking sheet designed at the Institute of Psychiatry, Ain Shams University. It includes detailed personal, family, medical and past history records.

**2) Revised Behavior Problem Checklist (R-BPC) (Quay and Peterson 1987):**

This questionnaire was translated to Arabic by ***Abou EL Ela, et al., 1998***. The questionnaire was applied to the mother of every child to answer all the items. The number of the items is 99. The questions consist of groups which are finally collected to give a score for a specific behavior. The scales are:

i) Conduct disorder scale concerned with the misconduct of the child.

ii) Socialized aggression scale concerned with group aggressive behavior of the child.

iii) Anxiety withdrawal scale concerned with anxious mood and withdrawal reaction of the child.

iv) Attention scale concerned with the inattention and distractibility of the child.

v) Motor excess scale concerned with the hyperkinetic behavior of the child.

vi) Psychotic behavior scale concerned with the bizarre and psychotic behavior.

**The mothers of both the Conduct disordered and healthy children were subjected to the followings:**

**1) Semi-structured psychiatric interview:**

It was designed at the Institute of Psychiatry, Ain Shams University; it includes detailed personal, family and medical information.

**2) Parenting stress index (PSI):**

Parenting stress index was constructed in 1976. It is a screening and diagnostic assessment technique designed to yield a measure of the relative magnitude of stress in the parent child system ***(Abidin, 1990).*** This revised form is subdivided into child domain comparing 47 items constituting 6 subscales, parent domain comparing 54 items constituting 7 subscales, and 19 items constituting the optional life stress scale.

The test includes the following subscales:

**I- Child Domain Subscales:**

**i) Adaptability:**

It addresses the issue of how well a child handles change and transitions. High score makes mothering task more difficult by virtue of the child's inability to adjust in his or her physical or social environment.

**ii) Acceptability of the child by parent:**

This variable addresses the issue of how close the child is to the parents' idealized or hoped for the child. High score means the child possesses physical, intellectual and emotional characteristics which do not match the parents' hope for the child.

**iii) Child demandingness:**

This refers to the direct pressure the child places on the parent. High scores are produced when the parent experiences the child as placing many demands upon him or her.

**iv) Child mood:**

Child characteristic stresses associated with mood are primarily related to excessive crying, withdrawal and depression. High scores are associated with children whose affective functioning shows evidence of dysfunction.

**v) Child distractibility/hyperactivity:**

This indicates that child distractibility and hyperactivity stresses result in a continuous drain on the parents' energy requiring not only active parental management but sustained high states of vigilance.

**vi) Child reinforces parent:**

It represents the degree to which the parent child interaction results in a positive affective response in the parents. Parents who earn high scores on this subscale do not experience the child as a source of positive reinforcement. Child characteristic domain score as a sum of the previously mentioned 6 subscales is also considered.

High scores = 122 or above are associated with children who display qualities that make it difficult for parents to fulfill the parenting process.

### II- Parent Domain Subscales:

#### i) Parent depression:

It assesses the extent to which the parents' emotional availability to the child is impaired and the extent to which the parents' emotional and physical energy is compromised. The scale also captures to some degree the punishing impact of guilt upon the parent.

#### ii) Parent attachment:

This scale was designed to assess the intrinsic investment the parent has in the role of parent.

#### iii) Restriction of role:

It addresses the impact of parenthood on the parents' personal freedom and other life roles. The scale assesses primarily the negative impact, losses, and sense of resentment associated with the parents' perceptions of loss of important life roles.

#### iv) Parent sense of competence:

This subscale is related to depression subscale, in assessing the extent to which the parents' emotional availability to the child is impaired.

#### v) Social isolation:

Parents who earn high scores in this subscale are under considerable stress and it is necessary to establish an intervention program as soon as possible.

#### vi) Relationship with spouse:

Parents who earn high scores on this subscale are those who are lacking the emotional and active support of the other parent in the area of child management.

#### vii) Parental Health:

This is suggestive of deterioration in parental health which may be either the result of parenting stress or may be an additional independent stress in the parent child system.

The parent domain score as a sum of the previously mentioned 7 subscales is also considered. High score: = 153 or above suggests that the sources of stress and potential dysfunction of the parent - child system may be related to dimensions of the parent functioning.

### III- Life Stress Optional Scale:

Parents who earn raw scores of 17 or above find themselves in stressful situational circumstances, which they consider beyond their control. In effects, high life stress scores tend to intensify the total stress the parent is experiencing.

## Statistical Analysis:

Qualitative variables were described in number and percentages and mean ± standard deviation (SD) if quantitative. Student t and ANOVA tests were used when comparing quantitative data between 2 or more than 2 groups respectively. Pearson correlation coefficient was used as an indicator of correlation between 2 quantitative variables. P value was always set at 0.05. All data manipulation and statistical analyses were performed using SPSS (Statistical Package for Social Sciences) version 11.

## Results:

Thirty children fulfilling criteria for conduct disorder according to DSM IV with there biological mothers were enrolled into the study.

Table (1) describes their main sociodemographic characteristics.

40% of the children were younger than 10 years and 60% older than 10 years. Nearly two thirds of the mothers (64.3%) were younger than 35 years and either illiterate or have a low level of education. Only 4 mothers (14%) were working for cash. Regarding fathers' age (53.3%) was older than 40 years. the total number of sibs in the family did not exceed 4 in (73.3%) of the sample.

Table (3) presents the correlation between the (R-BPC) items and PSI main domains and subscales and life stress index. Only 2 items on R-BPC correlated positively and significantly with the parent domain of PSI namely conduct scale which correlated with social isolation (r=0.531, P<0.05) and anxiety withdrawal which correlated with depression (r=0.609, P<0.05). Regarding correlation with the child's domain on the PSI, conduct scale and psychotic behavior as well as motor excess all correlated positively and significantly with distractibility (r= 0.707, 0.607, 0.576 respectively P<0.05) and acceptability (r= 0.513, 0.610, 0.530 respectively P<0.05). Attention problem with adaptability and mood (r= 0.630, 0.605 respectively P<0.05), anxiety withdrawal with demandingness (r= 0.568 P<0.05). The total child domain scores correlated positively and significantly with conduct scale (0.691, P<0.05), attention problem (0.581, P<0.05), psychotic behavior (0.723, P<0.05) as well as motor excess (0.601, P<0.05).

As shown in table (4) demandingness on the child domain correlated positively and significantly with all the parent domain scales except social isolation and relation to spouse. Acceptability correlated in the same way with parental attachment, restricted roles, depression and sense of competence. Both adaptability and reinforcement correlated positively and significantly with parental attachment and restricted roles. Mood on the other hand correlated similarly with parental attachment and restricted roles and with health in addition. Distractibility did not correlate with any of the parent subscales. It is worth noting that demandingness, mood and acceptability all correlated positively ands significantly with total parent score.

It was found that the higher the score in the parent domain the younger the age of the child at onset of treatment (r= -0.595, P<0.05). Health subscale was the most responsible (r= -0.59, P<0.05). It is worth mentioning that within the parent domain subscales, social isolation correlated positively and significantly with duration of illness (r= 0.636, P<0.05) and that relation to spouse correlated negatively and significantly with duration of treatment (r= -0.590, P<0.05).

Regarding total child domain scores, it was found that the higher the scores, the younger the age of the mother (r= -0.562, P<0.05) and the earlier the age of marriage (r= -0.577, P<0.05)

Individual child domain subscales summarized in table (5) showed:

Reinforcement correlated positively and significantly with age of the child and age in the study and his age at onset of treatment and negatively and very significantly with age of father and age of mother.

Demandingness correlated negatively and significantly with age of mother at marriage.

Adaptability correlated negatively and very significantly with age of mother in the study and at marriage.

Distractibility correlated positively and significantly with duration of illness and duration of treatment On the other hand life stress subscale correlated negatively and significantly with each of age of the child (r= -0.727, P<0.05), age of mother (r= -0.571, P<0.05), age of onset of illness (r=-0.505, P<0.05), age of child at onset of treatment (r= -0.674, P<0.05) and number of sibs (r= -0.490, P<0.01)

**Table (1): Child and Parents Characteristics of the Studied Sample**

| **Characteristics** | **Number (%)** |
|---|---|
| Child's Age | |
| - <10 | 12 (40.0) |
| - 10+ | 18 (60.0) |
| Mother's Age | |
| - < 35 years | 18 (64.3) |
| - 35+ | 10 (35.7) |
| Father's Age | |
| - <40 years | 14 (46.7) |
| - 40+ | 16 (53.3) |
| Education of the Mother | |
| - Illiterate | 12 (42.9) |
| - Prim/Prep | 6 (21.4) |
| - Secondary | 4 (14.3) |
| - High education | 6 (21.4) |
| Working Mothers | 4 (14.3) |
| Number of sibs | |
| - < 4 | 22 (73.3) |
| - 4+ | 8 (26.7) |
| Age of Mother at Marriage | |
| - <= 18 years | 14 (50.0) |
| - >18 | 14 (50.0) |

As shown in table (2), mean age of onset was 6.8 ± 3.5SD, mean duration of illness 2.5 ± 1.8SD, mean age at start of treatment 8.5±4.2, with a mean of 2.0 years' delay ±1.8SD.

**Table (2): Conduct Disorder History of Illness**

| Characteristics | Number (%) |
|---|---|
| Age of Onset | |
| =< 4 years | 4 (13.3) |
| 4 –5 | 4 (13.3) |
| 5 + | 22 (73.3) |
| Mean±SD | 6.8±3.5 |
| Duration of Illness | |
| Mean±SD | 2.7±1.8 |
| Age at start of Treatment | |
| Mean±SD | 8.5±4.2 |
| Delay from onset to treatment | |
| - At Onset | 4 (13.3) |
| - =< 1 year---- | 12 (40.0) |
| - > 1 yr --- | 4 (13.3) |
| - 3 years--- | 6 (20.0) |
| - 5 years+ | 4 (13.3) |
| Mean±SD | 2.0±1.8 |

Figure (1) shows the percentages of behavioral problems according to revised behavior problem checklist (R-BPC). Socialized aggression was the most frequently met (60%) followed by conduct scale (53.3%). On the other hand, anxiety withdrawal was the least frequently met (13.3%).

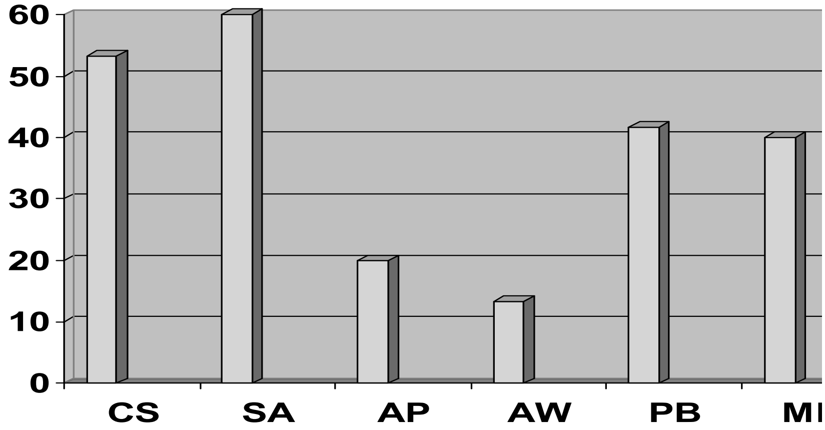
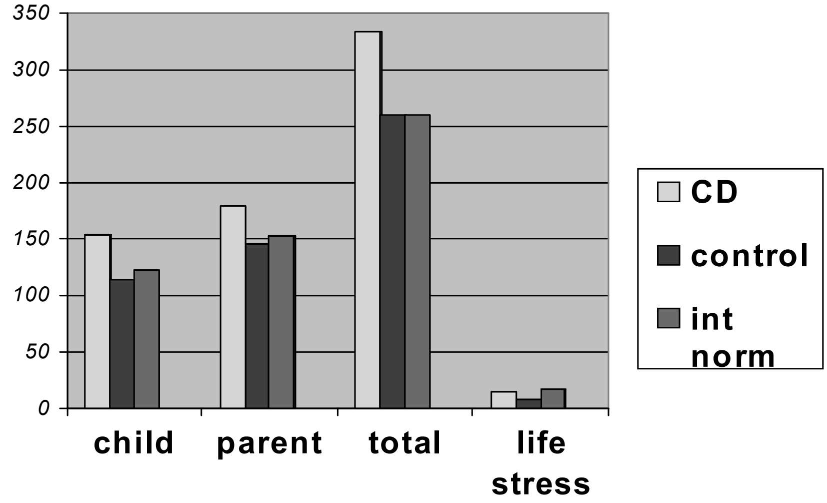
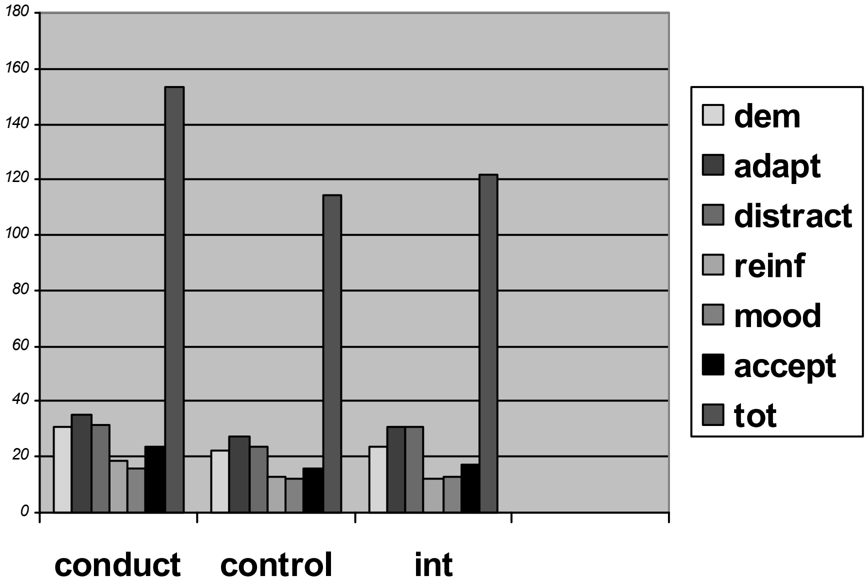


Fig. (1): CS= conduct scale, SA= social aggression, AP= attention problem, AW= anxiety withdrawal, PB= psychotic behavior, ME= motor excess

Figure (2) shows child, parent and total Parental Stress Index (PSI) scores in mothers of patients with conduct disorder in comparison with control group and international norms. In the total PSI scores, the conduct disorder group reported higher scores than the control group and the international norms while the median life stress score was higher internationally (17) than both CD (14.9) and control groups (7.7)



As shown in Figure (3) in all subscales of the child domain, CD group median values exceeded both the control group and the international norms



Regarding median parent domain subscales in the same sample, results are illustrated in figure (4)

For the parent domain subscales median scores were again higher than those of the control group as well as for the international norms.

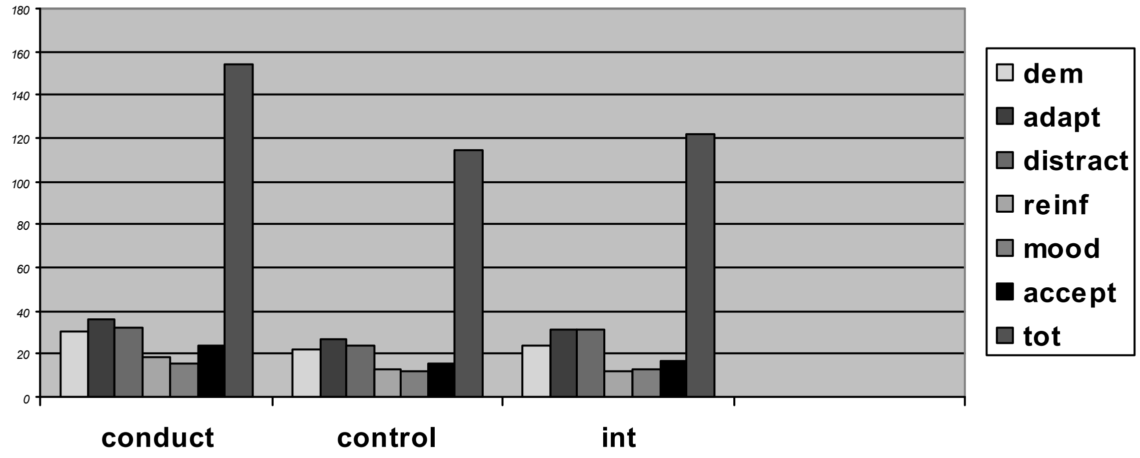


**Table (3) Correlation of (R-BPC) with PSI parents and child domains in CD patients:**

| Parenting Stress Domain Subscales | CBCL Items | | | | | |
|---|---|---|---|---|---|---|
| | CS | SA | AP | AW | PB | ME |
| **Parents Domain Subscales** | | | | | | |
| Health | 0.191 | -0.176 | 0.174 | 0.223 | -0.031 | 0.245 |
| Social Isolation | 0.531* | 0.445 | 0.109 | 0.399 | 0.249 | 0.100 |
| Parental Attachment | 0.097 | -0.001 | 0.416 | 0.292 | 0.305 | 0.308 |
| Restricted roles | 0.463 | -0.047 | 0.326 | 0.137 | 0.051 | 0.084 |
| Depression | 0.255 | 0.047 | 0.395 | 0.609* | 0.227 | 0.141 |
| Sense of Competence | 0.297 | 0.466 | -0.004 | 0.407 | 0.241 | 0.371 |
| Relation to Spouse | 0.103 | 0.008 | -0.025 | 0.371 | -0.142 | 0.447 |
| **Total Parent** | 0.303 | 0.086 | 0.182 | 0.362 | 0.242 | 0.404 |

**Table (3) continue:**

| **Parenting Stress Domain Subscales** | **CBCL Items** | | | | | |
|---|---|---|---|---|---|---|
| | **CS** | **SA** | **AP** | **AW** | **PB** | **ME** |
| **Child Domain Subscales** | | | | | | |
| Demandingless | 0.469 | 0.157 | 0.486 | 0.568* | 0.280 | 0.157 |
| Adaptability | 0.317 | 0.020 | 0.630* | 0.109 | 0.567 | 0.337 |
| Distractability | 0.707* | 0.095 | 0.402 | -0.027 | 0.607* | 0.576* |
| Child reinforces parents | 0.340 | 0.506 | 0.265 | 0.267 | 0.079 | -0.139 |
| Mood | 0.427 | -0.164 | 0.605* | 0.225 | 0.554 | 0.426 |
| Acceptability | 0.513* | 0.243 | 0.383 | 0.150 | 0.610* | 0.530* |
| **Total Child** | 0.691* | 0.262 | 0.581* | 0.303 | 0.723* | 0.601* |
| **Life Stress Score** | -0.120 | -0.309 | -0.078 | -0.197 | 0.172 | 0.251 |

CD=Conduct Disorder, SA=Social Aggression, AP=Attention Problem, AW=Anxiety Withdrawal, PB=Psychotic Behavior, ME=Motor Excess (*P<0.05)

**Table (4): Correlation of PSI parent's domain subscales child domain subscales**

| **Parent Domain Subscales** | **Child Domain Subscales** | | | | | |
|---|---|---|---|---|---|---|
| | Dem. | Adapt. | Distrac. | Reinf. | Mood | Accept. |
| Health | 0.702* | 0.416 | 0.205 | 0.213 | 0.641* | 0.338 |
| Social Isolation | 0.472 | 0.044 | 0.404 | 0.434 | 0.281 | 0.488 |
| Parental Attachment | 0.639* | 0.748* | 0.259 | 0.521* | 0.569* | 0.575* |
| Restricted roles | 0.632* | 0.535* | 0.429 | 0.529* | 0.582* | 0.605* |
| Depression | 0.533* | 0.354 | 0.279 | 0.349 | 0.497 | 0.611* |
| Sense of Competence | 0.658* | 0.367 | 0.339 | 0.431 | 0.384 | 0.578* |
| Relation to Spouses | 0.512 | 0.204 | 0.108 | 0.033 | 0.448 | 0.469 |
| **Total parent** | 0.748* | 0.509 | 0.413 | 0.321 | 0.609* | 0.639* |
| **Life Stress** | 0.054 | 0.119 | 0.135 | -0.386 | 0.108 | -0.052 |

Dem.=Demandingness, Adapt.=Adaptability, Distrac.=Distractability, Reinf.=Reinforcement, Accept.=Acceptability. (*P<0.05)

**Table (5): Correlation of PSI Child Domain Subscales with different socio-demographic history of illness variables**

| | Child Domain | | | | | |
|---|---|---|---|---|---|---|
| | Dem. | Adap. | Dist. | Reinf. | Mood | Accep. |
| Age of Child | -0.106 | -0.249 | -0.115 | 0.575* | -0.329 | -0.003 |
| Age of Onset | -0.184 | -0.239 | -0.353 | 0.396 | -0.391 | -0.101 |
| Age of Father | -0.306 | -0.156 | -0.238 | -0.447 $^{o}$ | 0.053 | -0.030 |
| Age of Mother | -0.446 | -0.463 $^{o}$ | -0.533* | -0.184 | -0.433 | -0.294 |
| Age of Mother at Marriage | -0.564* | -0.472 $^{o}$ | -0.279 | -0.492 $^{o}$ | -0.250 | -0.213 |
| Number of Sibs | -0.090 | -0.230 | -0.146 | 0.025 | -0.143 | 0.000 |
| Duration of Illness | 0.218 | 0.102 | 0.507* | 0.177 | 0.268 | 0.243 |
| Age of Child on Treatment | -0.512 | -0.219 | -0.191 | 0.575* | -0.476 | -0.074 |
| Onset to Treatment Duration | -0.181 | 0.184 | 0.495 $^{o}$ | 0.021 | 0.190 | 0.085 |

* P=<0.05 (Statistically Significant) $^{o}$ P=<0.10

## Discussion:

Understanding the genetic basis for behavior has fascinated the field of psychiatry for the past two decades. However, in this decade, it is again becoming apparent that understanding salient social environments, particularly early adverse caregiver/offspring relationships, is also necessary to the understanding of psychiatric disorders.

Childhood conduct disorder is a top mental health priority (Bethesda, 1998). Evidence from prospective longitudinal data shows that childhood conduct disorder precedes a variety of major axis I psychiatric disorders (Kim-Cohen 2003), suggesting that treating conduct disorder might significantly reduce the burden of adult mental disorder.

According to research cited in Phelps & McClintock (1994), 6% of children in the United States may have conduct disorder. The incidence of the disorder is thought to vary demographically, with some areas being worse than others. For example, in a New York sample, 12% had moderate level conduct disorder and 4% had severe conduct disorder. Since prevalence estimates are based primarily upon referral rates, and since many children and adolescents are never referred for mental health services, the actual incidences may well be higher (Phelps & McClintock, 1994).

Children who exhibit these behaviors should receive a comprehensive evaluation. Many children with a conduct disorder may have coexisting conditions such as mood disorders, anxiety, PTSD, substance abuse, ADHD, learning problems, or thought disorders which can also be treated. Research shows that youngsters with conduct disorder are likely to have ongoing problems if they and their families do not receive early and comprehensive treatment. Without treatment, many youngsters with conduct disorder are unable to adapt to the demands of adulthood and continue to have problems with relationships and holding a job. They often break laws or behave in an antisocial manner.

High levels of stress and emotional maladjustment are associated with being the parent of a child with a disruptive behavior disorder (Shaw, Winslow, Owens & Hood, 1998). Contextual stressors such as single parenthood (Webster-Stratton, 1985), financial insufficiency, marital conflict and intrapersonal stressors such as anxiety and depression, add to the hardships of rearing a child with behavioral problems. Stress affects parental emotions and behavior, disrupting parent-child interaction and affecting parental perceptions of child behavior (Webster-Stratton, 1990).

Did parents of conduct children manifested any form of stress related to their child's condition? That was the question addressed to be answered by this study. The majority of study children (60%) were above 10 years old and (40%) were below 10 years with mean age of onset 6.8 years and an average of 2 years delay from onset of symptoms till onset of treatment. These results are in agreement with most of the national and international studies (Sayed et al 2005 & Maughan et al 2004).

The prolonged delay in seeking treatment from the onset of symptoms may be attributed to different factors. To start with, parents in Egypt are able to tolerate the child's behavior and usually they consider the symptoms of conduct in their child as a sign of being an active and a smart child. Secondly, parents are always reluctant to seek psychiatric advice for their children because of the stigma of both mental illness and psychiatric treatment. The present results revealed that the majority of conduct children (60%) presented with socialized aggression, followed by conduct scale (53.3%). These findings were consistent with most of the studies, which detected similar frequencies (Conner et al 2006).

Assessment of conduct children's mothers revealed that the majority (about two thirds) were younger than 35 years old, either illiterate or have low level of education, housewives and total number of sibs in the family didn't exceed 4 in (73.3%) of the sample taken. The central finding of the present study is that mothers of conduct children experienced a significantly higher parenting stress more than both control group and international scores, this included the total score and both the child and parents domains. In addition, mothers of conduct children showed higher life stress score than the control group, while the life stress score was higher internationally. These findings are supported by Shaw et al 1998, who mentioned that parents of children with conduct experienced more parenting stress than parents of other children.

Moreover, this study revealed that in all subscales of child domain, the scores of mothers of conduct group exceeded both the mother of the control and international scores. These subscales include the adaptability, acceptability of the child to parent, child demandingness, child mood, child distractibility/hyperactivity, and child reinforces parent. This means that conduct children display qualities that make it difficult for parents to fulfill the parenting process and have negative impact on parents and with increasing parenting related stress (Shaw et al 1998, Routh et al 1995).

In addition, studying the parent domain subscales revealed that mothers of conduct group exceeded the control group in all subscales. These subscales include parent depression, parent attachment, restriction of role, parent sense of competence, social isolation, relationship with spouse and parental health. The high scores suggest that the sources of stress and potential dysfunction of the parent-child system may be related to dimensions of the parent's functioning, Wahler and Dumas (1989) have reported that the presence of stressors is associated with diminished parental attention to the child. Stress also leads to disruption of effective monitoring which is thought to be important in the prevention of problem behavior (Dishion & McMahon, 1998).

It is worth mentioning that the scores are even higher on the parent domain than those obtained in a previous study on parents of ADHD patients where total parent score of ADHD=163.45±22.6, while those of CD=180±23.8 especially due to higher scores on social isolation and sense of competence. Whereas, on the child's domain scores were nearly similar being 159.55±16.8 for ADHD as compared to 153.7±25.0 for CD (Sayed et al, 2005). This difference between both samples draws the attention to the weight of stigma and sense of responsibility for the CD child's misbehavior that are indicated by social isolation and sense of competence on parental stress and for the importance of discussing those issues with parents during therapy.

Negative mood and irritability related to mood disorders may also disrupt disciplinary practices (Conger, Patterson and Ge, 1995).The experience of multiple stressors over time leads to the development of disturbed schema of what is appropriate in child behavior. There is an over attribution of negative intent to the child, self-blaming when children do not comply, and feelings of defeat and anger (Stern & Azar, 1998). A number of models have been developed that predict how stress influences parental behavior (Abidin, 1992; Belsky, 1984; Conger et al. 1995; Webster-Stratton, 1990).

This study highlights the risk factors, which could contribute to the parenting stress among mothers of conduct children. Conduct disorder, anxiety withdrawal, psychotic behavior and motor excess were positively correlated to the total child domain score ($P<0.05$). In addition, conduct scale and psychotic behavior as well as motor excess all correlated positively and significantly with distractibility and acceptability while attention problem is correlated positively with adaptability and mood and anxiety withdrawal with demandingness. These findings come to be in agreement with another study that showed also similar correlations but with children having attention deficit hyperactivity disorder (Sayed et al 2005).

Demandingness and acceptability on the child domain correlated positively and significantly with all the parent domains scales except social isolation and relation to spouse. Mood on the other hand correlated similarly with parental attachment and restricted roles and with health in addition. It is worth noting that demandingness, mood and acceptability all correlated positively and significantly with total parent score.

It is well established that many conduct children have co-occurring ADHD and it is quite possible that these co-occurring behavioral problems, are the reasons for increased stress in parents of children of conduct disorder (Podolski et al 2001).

Social aggression and psychotic behavior were more manifested in conduct children when mother is of low educational level and when she gets married at an earlier age. The above mentioned factors were found to be implicated in the etiology of disruptive behavior in children by other researchers.

**Summary and implications**:

This study suggests that for mothers, parenting a conduct child is a stressful event that has a great implication on mother's parenting abilities. The maternal distress was experienced in all dimensions of the parent's functioning including parent's sense of competence, restriction of role, social isolation, and parental attachment relationship with spouse, parental health and parent depression. The maternal distress was predicted by the presence of inattention, hyperactivity, psychotic behavior, anxiety withdrawal, duration of the illness, delay to start treatment, age of the child and mother's education. Helping parents of children with oppositional deficit disorder (ODD) to cope more successfully with their disturbed cognitions, brought about by their own mental health problems and stressful lifestyle, may enable them to be more emotionally available and deal more effectively with their children. Based on the above, it was hypothesized that a parenting group that focused more on modifying parental Cognitions, problem solving skills and management of stress, in contrast to discipline and behavior management, would be more effective for clinically-referred children and will improve the treatment outcome in Conduct children .

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# Shyness in Arab Countries: Is it a physiological or Pathological Phenomena?

*Abd Al Razek G., Rashad, M. and Almanasef A.*

## Abstract:

To differentiates between physiological and pathological shyness. Finding their prevalence in a community sample in two different Arab country and lastly, comparing shyness and related psychiatric symptoms as avoidant personality symptoms and social phobia symptoms in the two countries. We examined a community sample of two groups, each consisted of 76 college student from Egypt and Saudi Arabia. All Participants assessed using Shyness scale (Al-Driny 1980), Fear of negative evaluation scale, an Arabic version of Social phobia Scale (Raulin & Wee, 1994), (Desoky., 2004) and Diagnostic Check list of Personality disorders (Rashad, 2000) for Avoidant personality. Further assessment for subjects with high score in the personality check list using Arabic version of Structured clinical interview for diagnosis of Personality disorder (SCID) (Mphtah,1994). Results: 9.8% of the Egyptian sample had pathological shyness with mean score of 61.5.+/-9.2 while it was 18.4 % in the Saudi sample with mean score of 62.2+/-12.3. At the same time high score in social phobia scale and presence of avoidant personality disorder highly associated with pathological shyness. There were no significant differences between both group regarding mean score of different scales. Though a number of cases of avoidant personality disorder and high score in social phobia were higher in Saudi group. Although in some culture shyness is a physiological phenomenon, which is socially accepted and expected, but there is another type of shyness, which is a pathological phenomenon that mostly related to avoidant personality and social phobia symptoms whether it represent the same or different psychopathology. The answer needs a lot of researches.

## Introduction:

Chronic shyness has been defined as a fear of negative evaluation accompanied by emotional distress or inhibition which interferes significantly with the participation of desired activities and with the undertaking of personal and professional goals **(Henderson, 1994)**. At the same time shyness has long been described as a character trait, an attitude, or a state of inhibition **(Lewinsky, 1941).** Another way of classification of shyness in two domains, fearful shy individuals versus self-conscious shy individuals. In the former group, fear of novelty and autonomic reactivity was hypothesized to be the major component. In the latter group, excessive awareness of public aspects of one's self was the central element **(Buss, 1985).** The definition of shyness also encompasses several of the central components found in social phobia, including fear of negative evaluation, interference with functioning, and negative cognitions. Comparing shyness, social phobia and avoidant personality disorders has been somewhat difficult due in part to the fact that shyness, a trait term, is part of common language as well as a psychological construct from personality theory research, rather than a formal DSM **(APA, 1987; APA, 1994)** category, like social phobia and avoidant personality disorder which is derived from researches with clinical samples **(Lorant et al., 1999). Henderson, 2004** found that, shyness occurred in 49% of the population, becoming disabling in 13% or more. Clinical observation suggests that individuals seeking treatment for shyness are in significantly greater distress than the general population, showing greater depression, generalized anxiety, social avoidance, interpersonal sensitivity. Recently the increased pervasiveness of both shyness and social phobia in the general population should be a source of concern, some suggest that shyness and social phobia are the same and should be treated as a medical condition with medication such as Paraoxitin, may be different from each other only in degree **(Carducci, 2000; Schrof & Schultz, 1999).** In Arab culture shyness is acceptable phenomena even some times may be expected. Are we in need for a shyness clinic with psycho-social intervention programs as that present in some western countries? A question needs an answer. As overlap between shyness, social phobia and avoidant personality disorder are quite common. So we tested the hypothesis that, There are two type of shyness physiological that is not accompanied by psychiatric symptoms and doesn't cause disability or need treatment and pathological shyness that associated with psychiatric symptoms and disorders as social phobia and avoidant personality. So our objectives are:

1. Differentiates between physiological and pathological shyness and finding their prevalence in a non clinical sample.
2. Finding the relation between pathological shyness, social phobia symptoms and avoidant personality disorder.
3. Compare shyness and related symptoms in two different Arab countries.

## Subjects and method

We examined a non clinical community sample of two groups; each consisted of 100 volunteers although upon data analysis only 76 of each group were suitable for analysis, as there were many dropouts, as some did not answer the whole questionnaire. First, one consisted of 76 Egyptian volunteers, selected from 5th year of faculty of medicine together with 2nd year of faculty of literature. The second group consisted of 76 Saudi volunteers; all were college students selected from 3rd grade of faculty of scientific health. Both male and female with age range 18-23 years. All of them accepted to join in the study after full information about the study.

### Tools:

1. Shyness scale which is a 36 statements Arabic scale each statement had 3 options for answers(each has specific score) and the total score achieved via algebraic sum of the whole 36 answers, the scale was constructed and validated in Arab countries with high internal consistency and reliability **(Al-Driny 1980)**
2. An Arabic version of Fear of Negative Evaluation scale, 30 statements scale, with yes or no answers with high validity and reliability in Arab countries **(Watson & friend, 1996) (Desoky, 2004).**
3. An Arabic version of Social phobia Scale **(Raulin & Wee 1994) (Desoky., 2004)** 36 items scale with yes or no answers and the total score achieved via algebraic sum of the whole 36 answers, the scale is constructed and valid in Arab countries, too.

4. Diagnostic Checklist of Personality disorders **(Rashad, 2000)** for Avoidant personality.
5. Arabic version of structured clinical interview for diagnosis of Personality disorder (SCID) **(Mphtah, 1994)** for further assessment of subjects with high score in the personality check list.
6. Written informed consent.

**Study proper:**

This is a cross-sectional observational study performed in the period from the September 2005 to Mai 2006. Every Participant received a file folder containing an informed consent statement and a copy of the following scales, shyness scale **(Al-Driny 1980),** An Arabic version of Fear Of Negative Evaluation scale **(Desoky., 2004),** an Arabic version of Social phobia Scale **(Desoky., 2004)** and Diagnostic Checklist of Personality disorders **(Rashad, 2000)** for Avoidant personality. Further assessment for subjects with high score in the personality check list using Arabic version of Structured clinical interview for diagnosis of Personality disorder (SCID) **(Mphtah, 1994).**

**Statistical methods**

The results analyzed using SPSS Version 10 Statistical program.

The following statistical procedures used in this work.

1. Logistic t test used for comparison between two mean groups.
2. Ranked Sperman Correlation Test to study the association between each two variables among each group.
3. Wilcoxon Rank sum test for comparison of qualitative values
4. Chi squared test to compare 2 proportions.

**Results:**

Regarding socio-demographic data there was no significant difference between Egyptian sample and Saudi sample regarding age, as age range 18-23 years with mean age of Egyptian as 20.1+/-1.4 and of Saudi as 19.7+/-1.5. In the same time no significant difference between both groups regarding sex as 51% of Egyptian sample were male versus 44.7% of Saudi sample. On the other hand 49% of Egyptian sample were female versus 55.3% of the Saudi sample.

**Table (1): Physiological and pathological shyness in both groups:**

| **Shyness** | **Egyptian group** | | **Saudi group** | | **Total** | | **significance** |
|---|---|---|---|---|---|---|---|
| | No | % | No | % | No | % | |
| **Physiological** | 69 | 90.2% | 62 | 81.6% | 131 | 85% | .182 |
| **Pathological** | 7 | 9.8% | 14 | 18.4% | 21 | 15% | |

- No statistical significance difference between both groups regarding prevalence of both type of shyness.

**Table (2): Correlation between shyness and other scales in both groups:**

| | **Age** | | **Social phobia scale** | | **Fear of negative evaluation scale** | |
|---|---|---|---|---|---|---|
| | **r** | **P** | **r** | **P** | **r** | **P** |
| **Egyptian** | -.223 | .115 | .581 | .000 | .462 | .001*** |
| **Saudi** | -.043 | .711 | .787 | .000 | .400 | .000*** |
| **Whole sample** | -.104 | .243 | .710 | .000 | .430 | .000*** |

There were very highly significant direct correlation between Shyness, Social phobia scale and fear of negative evaluation scale in both groups.

**Table (3): Relation between shyness and Avoidant personality symptoms and disorder in both groups:**

| | **Avoidant personality symptoms** | **Avoidant personality disorder** |
|---|---|---|
| | **P** | **P** |
| **Egyptian** | .062 | .023* |
| **Saudi** | .000*** | .000*** |
| **Whole sample** | .032* | .012* |

- There was significant relation between shyness and avoidant personality disorder in Egyptian group.
- There were very highly significant relation between shyness and avoidant personality symptoms and disorder in Saudi group.
- There were significant relation between shyness and avoidant personality symptoms in whole sample

**Table (4) Risk factors for pathological shyness: (regression analysis)**

| | **t** | **Significance** |
|---|---|---|
| **Fear of negative evaluation** | .173 | .863 |
| **Social phobia** | 5.052 | .000*** |
| **Avoidant Personality symptoms** | 1.394 | .166 |
| **Avoidant Personality disorder** | 6.992 | .000*** |

- High score on social phobia scale and presence of avoidant personality disorder considered as risk factors for pathological shyness.

**Table (5): Comparison between Egyptian and Saudi regarding all scale:**

| | **Shyness** | **Social phobia** | **Fear of negative evaluation** |
|---|---|---|---|
| | **M+/-SD** | **M+/-SD** | **M+/-SD** |
| **Egyptian** | 61.5+/-9.2 | 11.1+/-7.7 | 14.7+/-4.2 |
| **Saudi** | 62.2+/-12.3 | 8.7+/-7.5 | 15.3+/-4.2 |
| **Significance** | .677 | .081 | .467 |

- There were no significant differences between both groups regarding mean scores .

**Table (6) Comparison of both groups regarding pathological cases**

| | **Social phobia** | | **Avoidant personality symptoms** | | **Avoidant personality disorder** | |
|---|---|---|---|---|---|---|
| | low | **High** | **Low** | **High** | **No** | **Yes** |
| **Egyptian** | 86.1% | 13.9% | 74.5% | 25.5% | 94.1% | 5.9% |
| **Saudi** | 81.6% | 18.4% | 57.9% | 42.1% | 88.2% | 11.8% |
| **Sign** | .467 | | .055 | | .260 | |

-No statistical significance difference regarding prevalence of pathological cases in both groups.

**Table (7): Gender differences regarding different scales:**

| | **Shyness** | | **Social phobia** | | **Fear of negative evaluation** | |
|---|---|---|---|---|---|---|
| | **Male** | **Female** | **Male** | **Female** | **Male** | **Female** |
| **Mean score** | 58.8 | 64.7 | 8.1 | 11 | 15.3 | 14.9 |
| **Z** | -2.806 | | -1.767 | | -.506 | |
| **P** | .005*** | | .077 | | .613 | |

There was very highly significant gender difference regarding mean score of shyness as it was more among females.

## Discussion:

The prevalence of pathological shyness in the whole sample is 15% versus 85% physiological shyness. Although no statistical significant difference between both groups, regarding proportion of physiological and pathological shyness but number of cases with pathological shyness are higher in Saudi than Egyptian sample as there are 18.4% versus 9.8% respectively. In an older study by **Zimbardo et al. 1974,** they conducted a large- scale survey first with open-ended questions, then a self-report checklist which was administered to more than thousand people in the United States and many other countries, 40% reported being chronically shy; another 40% indicated that they had considered themselves as shy previously but no longer, 15% more as being shy in some situations, and only about 5% believed they were never shy. Since that time, the percentage of individuals reporting shyness has increased to nearly 50% (48.7% +/- 2) **(Carducci & Zimbardo, 1995).** Although they didn't differentiate physiological from pathological shyness may be as his sample taken from shyness clinic that is to say, mostly it indicate pathological type of shyness. In certain culture, shyness may be higher due to many cultural and religious factors that encourage development of physiological shyness. Another issue we searched for in our study is the relation between both type of shyness and other psychiatric symptoms related to shyness as, social phobia, fear of negative evaluation, Avoidant personality symptoms and disorder. Although there were very highly significant correlation between shyness, social phobia and fear of negative evaluation together with significant relation between shyness and avoidant personality symptoms and disorder but for pathological shyness only social phobia and avoidant personality disorder considered as risk factors or highly related to pathological shyness. Similar result found by **Bernardo et al., 2001,** who examine the relation between shyness, social phobia and social anxiety disorder in a non-clinical sample. Participants in the study completed the Cheek-Buss Shyness Scale (CBSS), Social Phobia Inventory (SPIN) and Liebowitz Social Anxiety Scale (LSAS). Internal correlational analyses (all p's < .05) indicated that the SPIN total score correlated with 18 of the 20 items of the CBSS. Of the 20 items of the CBSS, 17 correlated significantly with the fear/anxiety subscales of the LSAS while 13 correlated significantly with the LSAS avoidance subscale. On the other hand in this study comparing both group regarding all scales revealed no statistical significant differences regarding mean score while prevalence of pathological cases of avoidant personality disorder and high score of social phobia symptoms are higher at Saudi sample but they do not reach significance may be due to small sample size. However prevalence of social phobia differed from study to study and from culture to culture for example the National Comorbidity Survey of over 8,000 American correspondents in 1994 revealed a 12-month and lifetime prevalence rates of 7.9% and 13.3%. In another study carried on 2004, based on data from the 2002 Canadian Community Health Survey (CCHS), about 750,000 Canadians aged 15 or older, or about 3% of the population, reported that they had had symptoms of the disorder in the past year **(CCSF, 2002),** while in the same study, life time prevalence was 8%. As we see there are marked variability in the prevalence of social phobia from one study to another according to many factors which affect results as type of sample whether community sample, hospital based as shyness clinic, another factor is the number of sample, method of assessment and diagnostic criteria of assessment and time of the study whether old or recent Lastly cultural differences also may have an effect for example estimates of social phobia in East Asia are much lower than those in the West, with estimated lifetime prevalence in Korea of 0.5% **(Lee et al., 1990)** and in Taiwan of 0.6% **(Hwu et al., 1989).** Meanwhile our study, comparing prevalence of avoidant personality symptoms and disorder in both although it does not reach statistical significance but there are obviously high prevalence in Saudi sample. However 42.1% of the Saudi sample report high symptoms of avoidant personality while only 11.8% proved to have avoidant personality disorder after doing SCID, all of them having in addition pathological shyness. In the Egyptian sample they are 25.5% and 5.9% respectively. Data from National Epidemiologic Survey on Alcohol and Related Conditions (N = 43,093) show prevalence rate of APD of 2.36% **(Sarah 2006).** In addition regarding gender difference in our study scores are higher in all scales in females, although it does not reach significance except for shyness. Similar finding by **Chapman et al., 1995** who find social phobia higher among females as male to female ratio 3 to 2 respectively, however in the study of **(Carducci & Zimbardo, 1995)** they reported different pattern of shyness in both sex as for example, the frequency of gazing behavior. Furthermore, purely demographic variables may also play a role - for example there are possibly lower rates of social anxiety disorder in Mediterranean countries and higher rates in Scandinavian countries, and it has been hypothesized that hot weather and high-density may reduce avoidance and increase interpersonal contact **(Karen 2006**). On the other pole certain culture is pseudo sociophobic culture as the Japanese culture that promotes the sense of shame, "or one's awareness and sensitivity to the shame experienced by oneself or others" **(Okano, 1994).** Whether Arab culture is pseudo-sociophobic or not need further clarification? Although within the Arab, we have culture and subculture as, in Egyptian sample the pathological type of shyness that lead to disability and associated with social phobia symptoms and /or Avoidant personality disorder are nearly similar to that found in some western countries. While in the Saudi sample it may be higher, whether these are a reliable finding and indicate a cultural promotion for development of shyness or it is a bias in the study related to small number of sample or method of assessment, these may need further studies to be decided.

**Limitations of the study:**

- Small number of the sample
- Type of the sample
- Assessment method as we use Questionnaires to assess most of the variables which has less reliability than structured interview although most of community based studies use them especially that measure physiological phenomena as shyness.
- The social phobia scale is not a diagnostic scale but it measure traits indicating presence of pathology although we are not examining the prevalence of social phobia in our study.

## Conclusion:

Different cultures clearly have different definitions of what is normative interpersonally and socially. Cross-cultural studies on the prevalence of shyness have been done and indicate that there are differences in numbers across cultures, though the overall pattern of results indicates a universality of shyness across all cultures. What is important to remember in this regard is that a person's own definition of his/her degree of shyness may be at least somewhat dependent on the cultural background and ethnic identity **(Karen 2006).** In this study obviously there were two types of shyness physiological shyness which may be promoted in certain subculture and pathological shyness which is less prevalent, more disabling, associated with social phobia symptoms and avoidant personality symptoms and disorders.

## Recommendations:

- Additional researches need to be conducted on larger group of population in different Arab countries considering culture and subculture in every country to determine more accurately the prevalence of shyness whether physiological or pathological.

- Further research to determine clinical profile and cognitive characteristic of shyness in an attempt to establish more clearly the conceptual distinction and overlap with social phobia and avoidant personality disorders using different assessment tools. ,

- Shyness clinic is new term in Arab culture that may help some culture in treatment program of social phobia and related conditions together with helping in shyness researches.

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### الخجل فى البلاد العربية هل هو ظاهرة فسيولوجية أم مرضية

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# Cognitive Dysfunctions in Depressive Disorders

*Mahmoud A, Abelrazek G., Abdel Samee A. and Azzam H.*

## Abstract

The aim of our study was to find the cognitive dysfunction in unipolar depression and depressive phase of bipolar disorder and to compare both type of depression regarding clinical and neuropsychological findings. Several domains of cognitive function were examined in 22 depressed unipolar patients and 22 depressed bipolar patients diagnosed according to ICD10 research criteria, compared with 30 healthy volunteers. History and mental state examination done, using semi-structured interview, Hamilton depression rating scale for both patients group and subtests of WMSR together with Vigil continuous performance test for both patients and control to assess various aspects of memory and attention. There were highly significant cognitive impairment in immediate, short term and visual memory together with impairment in attention in both patients group relative to the control. On the other hand, visual memory span and vigil continuous performance test were more impaired in bipolar group. Mean while, there were no significant difference regarding both patients group in most of the compared parameters except for duration of illness and number of episodes which were more in bipolar group .Although bipolar depression is distinct from unipolar depression in terms of phenomenology , clinical characteristics and management but neuropsychological distinguishing is still not well established. In the same time whether unipolar or bipolar, depression is a chronic illness with chronic disability that may need new treatment modalities is still an area that may need further and further researches.

## Introduction

A long-standing scientific controversy with many clinical consequences is whether bipolar and unipolar disorder are the same or separate and distinct illnesses (*Hirschfeld, 2005).* In the late 19th and early 20th century, Kraepelin, in Germany, emphasized the distinction between dementia precox and manic-depressive insanity (*Kraepelin and Leipzig, 1893) (Kraepelin and Leipzig, 1896)*. One source of this dichotomy was the emphasis on moods versus cognition and will. However, the major rationale for the distinction was a perceived difference in clinical course and outcome. It was not until 1966 that bipolar disorder was described as separate and distinct in articles by *Jules Angst (1966),* Carlo Perris (Perris 1966) and Winokur and colleagues (Winokur, Clayton and Reich, 1969) in the United States. These articles proposed separation between unipolar and bipolar disorders based on difference in genetics, gender, clinical course, and premorbid personality *(Murphy and Sahakian, 2001).* Nowadays, although unipolar depression and bipolar depression are considered as distinct entities both by clinicians and researchers, it is not clear whether a pathophysiological distinction, which is the bridge between etiology and treatment, exists between these two conditions *(Lakshmi et al., 1997).*

Unavoidable practical considerations often interfere with ideal methodologies. First, researchers often neglect to indicate whether patients are in a manic, depressed or euthymic phase at the time of assessment. This is in part owing to difficulties with monitoring what are often rapid fluctuations in mood. Second, patients with bipolar disorder are generally receiving a combination of medications - including mood stabilizers, antidepressants, neuroleptics and benzodiazepines - that may or may not influence neuropsychological performance. Differences observed between patients and controls, or patients in different stages of bipolar illness, may be confounded by different medication regimens. *(Murphy and Shakan, 2001)*

Aiming to avoid some methodological difficulties in previous studies that search for cognitive dysfunction in depression and, or compare various types of mood disorders, our study conducted to compare unipolar depression with bipolar depression during acute episodes of depression using clinical data and neuropsychological tests.

**Objectives:**

1- To determine and compare the pattern of cognitive deficit in unipolar and bipolar depression
2- Compare unipolar and bipolar depression using both clinical and neuropsychological findings.

**Subjects and method**

44 patients between the age 18- 45 years, including 22 unipolar depression and 22 bipolar depression (during the depressive phase of bipolar disorder) as diagnosed according to ICD10-R criteria for mental illness compared with 30 healthy volunteers. The patients participating in the present study were selected from outpatient clinic or inpatients word of institute of psychiatry –Ain Shams University.

**Inclusion criteria:**

-Age: 18-40 years old

-Both males and females were included

- Fulfilling the criteria of diagnosis of unipolar major depression and bipolar depression according to the ICD-10 Diagnostic Criteria for Research.

- All during acute phase of the disorder

**Exclusion criteria:**

-Patients with below average intelligence.

-Patients below the age of 18 and above the age of 40.

-Patients with history of organic illness, head trauma, Dual diagnosis, or history of drug abuse disorder or on ECT.

**Control group**

The control group consisted of 30 Egyptian individuals with no apparent physical or psychiatric morbidity. They matched for age, sex, and other demographic variables as far as possible with the patient group. They have no family history of any psychiatric disorder selected from a pool of normal volunteers from the Hospital Clinics of Ain –shams university hospitals

**Tools:**

1. Clinical examination and history taking: Full history and examination using Ain Shams psychiatric interview sheet.
2. (ICD-10).ICD-10 Symptom Checklist of mental disorders for diagnosis: This is a semi-structured instrument for assessment of the psychiatric symptoms and syndromes in the F0-F6 categories of the ICD-10. *(Janka et al., 1994).*
3. 4- Hamilton rating scale for severity of depression: Hamilton scale is a standardized measure of the phenomenology of a depressive syndrome. Its score on 17 item ranging from 0-50, scores of 7 or less

considered normal; from 8-13 is considered mild; 14-18 is moderate; 19-22 is severe; and 23 and above is considered very severe. *Hamilton M (1960):*

4. General Health Questionnaire (Goldberg, 1983)): It is a self-administered questionnaire for the detection of mental disorders. There are 4 forms of GHQ: The scale of 28 items was used in its Arabic version

5. Neuropsychological Assessment:

The following tests were used for assessment of major areas of cognition:

***a)* The Wechsler Memory Scale-Revised (WMS-R) *(Wechsler, 1987).***

Comprehensive set of subtests measuring attention and encoding, retrieval, and recognition of various types of verbal and visual material with both immediate recall and delayed retention; excellent age-stratified normative comparisons for adults up to age 89, with intellectual data for direct comparison. Four of the eight subtests of the WMS-R that represent good assessment of memory were chosen to the present study, as follows: (a) Verbal Paired Associates: for assessment of immediate and delayed recall, (b)Visual Paired Associates: for assessment of immediate and delayed recall, (c) Digit span: It includes digit span forward, for assessing ability to process relatively simple information and digit span backward for more complex simultaneous processing and cognitive manipulation demands, (d) Visual memory span: The two parts of the visual memory span subtest, tapping forward and tapping backward, are administered separately.(test measure visual-spatial memory)

**b) Vigil continuous Performance Test:**

It is the most common research paradigm in cognitive studies of sustained attention and psychopathology. The two elements distinguished are; sensitivity and the response criterion. Diminished sensitivity is a sign of decreased vigilance and results in a high miss rate (errors of omission). The response criterion can be diminished leading to a high false positive rate (errors of commission). Reaction time is variable that represents the average time from the onset of each stimulus to the initiation of each response, Vigil requires only one response to one stimulus. More than one response in the inter-stimulus interval is defined as a perseveration.

### Study proper:

Our study was a case control study, which performed in the period from the February 2005 to August 2005. We include all patients presented within this period and fulfiling our inclusion criteria whether presented to Emergency room or outpatient clinic.The history and mental state examination performed using ICD10 symptom checklist by the psychiatrist using Ain Shams psychiatric interview sheet. After diagnosis, both patients group and control group gave written informed consent to participate in the study after the procedures fully explained. The Hamilton Depression Rating Scale done for both patients group to assess severity of the illness. The previously mentioned neuropsychological tests performed to both patients group and control .

### Statistical methods

The results analyzed using the Stat Open, Echo Soft Corporation, USA (2001) from Apple Mac.

The following statistical procedures used in this work.

1- Logistic t test used for comparison between two mean groups.

2- Ranked Sperman Correlation Test to study the association between each two variables among each group.

3- The probability of error (p) value was used to indicate level of significance as follows:

P>0.05: non significant, this occurs when (t) value is <1.7

P<0.05: significant, this occurs when (t) value is >1.7

P<0.01: highly significant, when (t) value is >2.3

P<0.001: very highly significant, when (t) value is >3.4

**Results**

**Table (1): Comparison between unipolar depression and bipolar depression regarding sociodemographic data**

| Social data | | Unipolar depressed Patients n=22 | | Bipolar depressed patients | |
|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD |
| Age | | 30.77 | 8.59 | 32.25 | 5.44 |
| sex | | No | % | No | % |
| | Males | 4 | 18.18 | 13 | 59.09 |
| | females | 18 | 81.81* | 9 | 40.90 |
| Marital status | Single | 8 | 36.36 | 11 | 50 |
| | Married | 14 | 63.63* | 11 | 50 |
| Level of education | illiterate | 1 | 4.54 | 4 | 18.18 |
| | Primary & preparatory | 10 | 45.45* | 5 | 22.72 |
| | Secondary | 7 | 31.81 | 5 | 22.72 |
| | university | 4 | 18.18 | 8 | 36.36* |

- In our sample 81.8% of unipolar depressed patients were females while in bipolar group males exceeding females about 59% were males

- Most of unipolar depressed patients were married 63.6% while in bipolar group was equal

- 50% of unipolar depressed patient were of low education or illiterate while only 41% of bipolar group were of low education or illiterate.

**Table (2): Comparison between unipolar depression and bipolar depression regarding history findings:**

| Subscale | | unipolar depressed patients | | Bipolar depressed patients | | T value |
|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | |
| Age of onset | | 27.14 | 8.56 | 24 | 6.32 | 1.38 |
| No of episodes | | 2.73 | 2.57 | 4.25 | 2.49 | -1.99* |
| Duration of last episode (month) | | 1.98 | 0.76 | 1.69 | 0.26 | 1.69 |
| Duration of illness (years) | | 3.63 | 3.88 | 8.25 | 4.33 | -3.73*** |
| Hamilton depression score | | 35 | 9.53 | 36.88 | 7.32 | -0.73 |
| Presence of stressor | | No | % | No | % | |
| | +ve | 19 | 86.36 | 20 | 90.90 | -3.95*** |
| | -ve | 3 | 13.63 | 2 | 9.09 | |

-There was a significant difference regarding number of episodes in both group as it was more in bipolar depressed patients (P value <0.05).

- Also duration of illness in years were significantly more in bipolar depression (P value ,0.001)

-In addition there was significant difference regarding presence of psychosocial stressor as it was more in Bipolar group ( P value <0.001)

**Table (3): Comparison between Unipolar depressed patient and control group as regard Wechsler memory scale revised:**

| Subscale | Unipolar depressed Patient n= 22 | | Control n=30 | | T value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Visual PA (immediate) | 11.23 | 4.17 | 14.00 | 2.33 | -3.05** |
| Verbal PA (immediate) | 16.68 | 2.85 | 19.37 | 2.50 | -3.16*** |
| Digit span | 11.68 | 2.71 | 13.17 | 3.40 | -1.69 |
| Visual memory span | 12.77 | 2.39 | 13.13 | 2.06 | -0.59 |
| Visual PA (short) | 4.27 | 1.52 | 5.00 | 0.98 | -2.10* |
| Verbal PA (short) | 5.86 | 1.32 | 7.03 | 1.10 | -3.49*** |

- There was a significant statistical differences between unipolar depressed patients and control group as regard score of visual and verbal paired associates I, II, and verbal paired associates II (short term memory), where patients had significantly lower score than control group.

**Table (4): Comparison between Unipolar depressed patients and control on total results of the continuous performance test**

| Subscale | Unipolar depressed Patients n=30 | | Control n=30 | | T value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Total Omissions | 8.14 | 8.11 | 2.77 | 1.92 | 3.51*** |
| Total Commissions | 11.14 | 10.33 | 3.27 | 2.66 | 4.01*** |
| Average delay | 501.18 | 53.42 | 522.98 | 39.28 | -1.70 |

- There were very highly significant statistical differences between both groups as regard total results of continuous performance test; where patients had higher score of total omission, and total commission, than the control group.

**Table (5): Comparison between Bipolar depressed patient and control group as regard Wechsler memory scale revised:**

| Subscale | Bipolar depressed Patient n= 22 | | Control n=30 | | T value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Visual PA (immediate) | 9.63 | 2.97 | 14.00 | 2.33 | -5.94*** |
| Verbal PA (immediate) | 15.13 | 3.18 | 19.37 | 2.50 | -5.38*** |
| Digit span | 10.88 | 1.81 | 13.17 | 3.40 | -2.86** |
| Visual memory span | 11.13 | 1.13 | 13.13 | 2.06 | -4.12*** |
| Visual PA (short) | 3.75 | 1.49 | 5.00 | 0.98 | -3.65*** |
| Verbal PA (short) | 5.88 | 1.13 | 7.03 | 1.10 | -3.70*** |

- There were highly significant statistical differences between both groups as regard score of visual and verbal paired associates I, II, and Digit span ,where patients had lower score than control group.

**Table (6): Comparison between Bipolar patients and control on total results of the continuous performance test**

| Subscale | Bipolar depressed Patients n=30 | | Control n=30 | | T value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Total Omissions | 17.63 | 11.45 | 2.77 | 1.92 | 7.00*** |
| Total Commissions | 12.5 | 10.38 | 3.27 | 2.66 | 4.68*** |
| Average delay | 537.28 | 52.98 | 522.98 | 39.28 | 1.12 |

- There was very highly significant statistical difference between both groups as regard total results of continuous performance test; where patients had higher score than the control group.

**Table (7): Comparison between Unipolar depressed patients and Bipolar depressed Patients group as regard Wechsler memory scale revised:**

| Subscale | Unipolar depressed Patient n= 22 | | Bipolar depressed patients n=22 | | T value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Visual PA (immediate) | 11.23 | 4.17 | 9.63 | 2.97 | 1.47 |
| Verbal PA (immediate) | 16.68 | 2.85 | 15.13 | 3.18 | 1.70 |
| Digit span | 11.68 | 2.71 | 10.88 | 1.81 | 1.15 |
| Visual memory span | 12.77 | 2.39 | 11.13 | 1.13 | 2.91* |
| Visual PA (short) | 4.27 | 1.52 | 3.75 | 1.49 | 1.15 |
| Verbal PA (short) | 5.86 | 1.32 | 5.88 | 1.13 | -0.05 |

There was highly significant statistical difference between both groups as regard score of visual memory span where bipolar depressed patients had lower score than unipolar one.

**Table (8): Comparison between Unipolar depressed patients and Bipolar depressed Patients on total results of the continuous performance test**

| Subscale | Unipolar depressed Patients n=22 | | Bipolar depressed patients | | T value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Total Omissions | 8.14 | 8.11 | 17.63 | 11.45 | -3.17* |
| Total Commissions | 11.14 | 10.33 | 12.5 | 10.38 | -0.44 |
| Average delay | 501.18 | 53.42 | 537.28 | 52.98 | -2.25* |

- There were highly significant statistical difference between both groups as regard total results of continuous performance test; where bipolar patients had higher score of total omission, and average delay, than the unipolar group.

**Discussion:**

There are numerous studies that compare unipolar and bipolar depression, finding the differences whether clinical, biological or both in order to explain why management should be different. In our study we try to find some of the differences using neuropsychological tests, as patients with depression frequently complain of memory difficulties, it is perhaps not surprising that these subjects demonstrate impairments on a range of memory tasks as proved by *Blaney, 1986; Johnson & Magaro, 1987; Burt et al, 1995*. Regarding socio-demographic data, there is no significant difference between both patient groups regarding age, however, since life time prevalence of unipolar depression is more among female 10–25% for women and 5–12% for men *(Blazer et al., 1994),* in fact this finding may explain why in our sample, although it is not a community sample but still most of unipolar group are female.

In addition there is statistically significant difference between both groups regarding educational level as 50% of unipolar are of low educational level or illiterate while 41% of bipolar are of low educational level or illiterate although this difference although statistically significant but clinically not significance.

On the other hand, regarding clinical characteristics of both groups, there are no significant difference between both groups regarding age of onset, duration of last episode and severity of illness as indicated by Hamilton depression rating scale. Since the age of the patients and severity of the last episode are nearly the same in both groups so any differences in cognitive function are not related to these factors which causes bias in previous studies as in the study of, *Savard et al (1980 )* as patients were significantly older than those in the unipolar group, suggesting that age alone may have accounted for their findings. Additionally, *Wolfe et al (1987)* cautioned that differences between their unipolar and bipolar groups might actually reflect subtle differences in severity.

Further more there is significant difference regarding duration of illness and number of episodes which are more in bipolar group. These differences between both group may causes some bias in our results. As in the study of Philippe et al., 2004 who found that the effects of the repetition of the depressive episodes were not modulated by the subtypes of depression and may reflect sensitization to the cognitive impact of depression associated with increasing prefrontal dysfunction. Although, Philip et al., were more interested in the severity of cognitive impairment rather than the profile of cognitive impairment.

Although patients with depression have been studied using a wide range of neuropsychological tests, researchers have focused on memory and executive function, ( Elliott, 1998). Deficits have been reported on tests of short-term memory, verbal and visual recognition memory, spatial working memory and immediate or delayed recall (Austin *et al*, 1992; Brown *et al*, 1994; Ilsley *et al*, 1995; Beats *et al*, 1996; Elliott *et al*, 1996). As such a broad spectrum of findings may suggest, there has been much debate over the precise nature of memory impairment, and a number of distinct formulations have been offered to explain the observed deficits (Robbins *et al*, 1992). Where as in our study comparison between unipolar depressed patients and control group revealed highly significant difference between both group as regard tests of immediate memory, tests of short term memory and tests of sustained attention. However no difference between unipolar depressed patient and control group regarding tests of visual-spatial memory and sustained attention.

On the other-hand comparing bipolar group patient to the same control group using the same tests revealed very highly significant difference between both groups allover the whole tests as patients has significant impairment in, immediate, short term, visuo-spatial, attention and sustained attention. These differences in profile and severity of cognitive impairment in bipolar group either related to their clinical characteristics or related to the effect of bipolar illness per se or both of them. Meanwhile, when comparing both patients group on subtest of Wechsler memory scale revised and Vigil continuous performance test revealed no significant difference between both groups regarding short-term memory, immediate memory or attention. However, the main differences are in the visual-spatial memory and sustained attention as bipolar group is worse. Therefore, according to these results, we can say both differences in clinical characteristics and subtype of depression may affect pattern and severity of cognitive impairment, although clinical characteristics may have the upper hand.

These results are similar to those found by Philippe et al., 2004 who examined three group of patients, group with first episode depression , group with recurrent major depression and last group with recurrent bipolar depression comparing them with healthy control group on a verbal episodic memory task. Patients suffering from a first depressive episode did not show verbal memory impairment as compared to normal controls. Unlike first episode patients, recurrent unipolar depression and bipolar depression patients exhibited verbal memory deficits with impaired free recall and normal cued recall and recognition.

The same results found by Bearden et al 2006 who stated that despite comparable general intellectual abilities, bipolar and unipolar patients exhibited significant memory deficits relative to healthy controls. A similar deficit profile was observed in both patient groups, involving visual memory, immediate and short term memory. These impairments were not secondary to strategic processing deficits or rapid forgetting, so their results suggest qualitatively similar patterns of memory impairment in bipolar and unipolar patients, consistent with a primary encoding deficit. These impairments do not appear to be secondary to clinical state, but rather suggest a similar underlying pathophysiology involving medial temporal dysfunction.

As has been noted, the only significant differences between both patient group in our sample are regarding visual-spatial memory and sustained attention as bipolar group are worse. These results agree with the study of *Borkowska and Rybakowski (2001), as they found that, neuropsychological* frontal lobe tests indicate that bipolar depressed patients are more impaired than unipolar. Again similar finding in the study *of Martinez etal, 2004*, as he found that clinical variables were associated with neuropsychological measures. As patients with a longer duration of illness showed more memory dysfunctions, more slowness or diminished attention. In-addition similarity in cognitive impairment found in our sample of unipolar and bipolar patients may agree with some of the findings of *Bearden et al, 2006* who found that bipolar patients show declarative memory impairments, in all phases of bipolar and independent of their current state (manic versus depressive).

Thus the questions about similarities and differences between unipolar and bipolar depression is still a persistent question in our study as we found many similarities regarding pattern of neuropsychological impairment and few differences between both patients group regarding profile and severity of cognitive function as we have said these may be related to both history findings and subtype of depression , as found by of *Bearden et al, 2006, Martinez et al, 2004, Philippe et al., 2004* and *Borkowska and Rybakowski (2001).* Furthermore the differences between our study and other studies may be related to, differences in sociodemographic data, clinical characteristics of the patients group and lastly the neuropsychological tests used. Although our studies and the other studies agree on that there are cognitive deficit in depression whether unipolar or bipolar mainly in memory, attention and sustained attention these impairment may be slightly more in bipolar patients regarding some aspects of cognitive functions. Also these impairment may related to certain clinical characteristics of the patients as duration of illness and number of episode rather than related to affective state as found by of *Bearden et al, 2006 and Martinez et al, 2004.*

Opposing the researcher's predictions, although bipolar depression is distinct from unipolar depression in terms of phenomenology, clinical characteristics and management but neuropsychological distinguishing is still not well established.

**Limitations:**

Unavoidable practical considerations often interfere with ideal methodologies, clouding and weakening conclusions drawn from the results of clinical neuropsychological studies. (*Murphy and Sahakian.2001)*

- First although the study tried to overcome methodological difficulties in previous researches by matching both group of patients and control as much as we can, but still difficult to say, we overcome all of it as some clinical characteristics of unipolar patients group were different from that of bipolar depressed group sample such as duration of illness, number of episodes. These clinical differences affect severity of the disorder and hence may affect results of neuropsychological tests.

- Second the neuropsychological tests performed in the study are not enough to determine the whole aspects of cognitive impairment in depression.

- Lastly both patients group were on pharmaco-therapy which may affect the results of neuropsychological tests.

Clinical implications:

- Our results indicate that, whether unipolar or bipolar, depression is a chronic illness with disability, although our study could not answer the questions whether these impairment in cognitive function is a trait, state or scar marker

- The presence of such cognitive dysfunctions indicate treatment noncompliance, and poor social outcome.

- Cognitive behavioral therapy and drugs which didn't interfere with cognitive functions are recommended in both unipolar and bipolar depression in order to minimize or at least did not aggravate these cognitive deficit.

## Future Directions

-More research is needed to study the difference between bipolar and unipolar depression using different neuropsychological and biological tasks.

- Further studies to determine whether these cognitive impairments are state, trait or scar marker.

- To study the effect of cognitive behavioral therapy and maintenance antidepressants on the prognosis of these cognitive deficits.

## Summary:

Although many studies have demonstrated the presence of wide-ranging neuropsychological deficits in patients with major depression, but only few of them study depressive phase of bipolar. In brief, we try to study cognitive function in both unipolar and bipolar depression during acute phase of both of them. Then comparing both types of depression in order to determine similarity and differences between them as regard neuropsychological deficit. As mentioned in the previous studies, cognitive impairment were present in both types of depression, pattern of these cognitive deficits may be slightly different in both types of depression these differences either related to clinical differences in the sample or biological differences between both types of depression.

## Conclusion

Depression is a chronic disorder which could affect social and cognitive function of the patients. This cognitive impairment may be related to a lesser extent to subtype of depression or phenomenology of depression but, the most important is the chronicity of the illness as shown in our study and some of the previous studies. Finally although unipolar depression is clinically distinguished from bipolar depression but yet many research needed to determine neuropsychological differences between both types.

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## اضطراب الوظائف المعرفية فى مرضى الاكتئاب

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# Metabolic syndrome and serum level of adiponectin in Egyptian patients with schizophrenia

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## Abstract

Metabolic syndrome is an important risk factor for cardiovascular morbidity and mortality in schizophrenic patients. In Egypt, however, its prevalence among these patients is uncertain. Also, little is known about the relationship between the metabolic syndrome and serum level of a substance such as adiponectin among Egyptian patients with schizophrenia, at a time when in other nations the usefulness of adiponectin for the prediction of insulin resistance and metabolic syndrome is attracting much attention.To assess the frequency of metabolic syndrome and the serum level of adiponectin in a sample of Egyptian outpatients with schizophrenia, testing the hypotheses that (a) the prevalence of the metabolic syndrome is higher among schizophrenic patients compared with a normal group of subjects, and (b) serum adiponectin level has an inverse relationship with the parameters of the metabolic syndrome in these patients. 50 consecutive out-patients with schizophrenia, classified into early illness (N= 26 patients) and chronic illness (N= 24 patients) groups, and a matched group of 100 apparently healthy controls were compared using the International Diabetes Federation (IDF) criteria and serum levels of adiponectin. 19 patients (28%) as opposed to five controls (5%) met the criteria of the metabolic syndrome. None of these patients or controls, however, was previously diagnosed or treated for this syndrome or for any of its components. Serum adiponectin level in the patients group was negatively associated with all the parameters of the metabolic syndrome except the HDL level with which it was positively associated. In the control group, however, there were no such significant correlations. Patients, classified by the type of antipsychotics, did not differ in the serum level of adiponectin, or in the prevalence of the metabolic syndrome and its parameters. The metabolic syndrome is highly prevalent among treated Egyptian patients with schizophrenia. Thus, assessment of the presence and monitoring of the associated risks of the metabolic syndrome should be part of the clinical management of such patients. In line with the mounting body of evidence in other populations, this study indicates that measurement of serum adiponectin level by ELISA technique may be a useful biomarker for the metabolic syndrome in schizophrenic patients.

## Introduction

There is an excess of death from natural causes among people with schizophrenia (Joukamaa et al., 2006; Mitchell and Malone, 2006) primarily due to cardiovascular disorders (Davidson, 2002; Van Gaal, 2006). One major risk factor for these disorders is the metabolic syndrome (Chen et al., 2006) which is reported to have a higher frequency among schizophrenic patients (De Hert et al., 2006; Heiskanen et al., 2003) and is receiving significant attention because of its high prevalence in the general population (approximately 24% in the United States) (Ford et al., 2002) and its role as an independent risk factor for cardiovascular morbidity and mortality (comparable to smoking) (Lamarche and St-Pierre, 2005; Tonstad and Svendsen, 2005). The syndrome was originally identified by Reaven (1988; 1992) as syndrome X or the insulin resistance syndrome for the clustering of cardiovascular risk factors like hypertension, glucose intolerance, high triglycerides and low HDL concentration, and has been given several other names, including the 'plurimetabolic syndrome', and the 'deadly quartet' (Kaplan, 1996). Associated with a 3 fold and 2 fold increase in type 2 diabetes and cardiovascular disease (CVD), respectively, it is thought to be a driver of the modern day epidemics of diabetes and CVD and has become a major public health challenge around the world (Zimmet et al., 2005). In 1998, WHO proposed a definition for the syndrome and chose to call it the 'metabolic syndrome' (Alberti and Zimmet, 1998). This name was chosen primarily because it was the cause of all the components of the syndrome. Since its initial description, several definitions of the syndrome have emerged. Each of these definitions used differing sets of criteria, which reflected contrasting views on pathogenic mechanisms and the need for clinical usefulness, e.g., the modification version of the WHO definition introduced by the European Group for study of Insulin resistance (EGIR) (Balkau and Charles, 1999) and the ATP-III definition introduced by the National Cholesterol Education Program (NCEP) of USA (National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2002). The use of these definitions to conduct research into the metabolic syndrome in diverse populations resulted in wide ranging prevalence rates, inconsistencies and confusion, and spurred on the vigorous debate regarding how the metabolic syndrome should be defined. In response to this controversy, the International Diabetes Federation (IDF) has recently proposed a new definition (Alberti et al., 2005), which is convenient to use in clinical practice and is applicable to populations around the world so that data from different countries can be compared (Alberti et al., 2006; Zimmet et al., 2005).

The mechanisms underlying the metabolic syndrome are not fully known, but thought to be multiple: among them, the adipose tissue excess is suspected to play a major role (Fasshauer and Paschke, 2003; Flier, 2001). Adipose tissue, in addition to its function as an energy storage depot, has been increasingly recognized as an important endocrine organ that secretes a large number of biologically active hormone-like peptides, named adipokines (Ahima, 2006). Among them are mainly leptin and TNF-$\alpha$ as pathogenic factors and adiponectin, also known as ACRP-30 (Scherer et al., 1995), Adipo-Q (Hu et al., 1996), apM1 (Maeda et al., 1996), or GBP28 (Nakano et al., 1996), as a protective factor (Moller and Kaufman, 2005). Experimental studies in mice have shown that intraperitoneal administration of adiponectin lowers plasma glucose (Combs et al., 2001). In humans, decreased plasma adiponectin levels have been demonstrated in patients with obesity and diabetes (Arita et al., 1999; Mannucci et al., 2003). Obesity is associated with the changes in the production of adipokines consisting of decreasing production of adiponectin and increasing production of leptin and TNF-$\alpha$, which step by step deteriorate the metabolic status (Lee and Pratley, 2005).

In Egypt, some of the basic components of the metabolic syndrome, e.g., diabetes mellitus and obesity, have become a focus of clinical attention in recent years. Diabetes, which was described for the first time in human history in Egypt (~1500 BC) has now become one of its major and emerging clinical and public health problem (Herman et al., 1995; 1998). By the year 2025, Egypt is expected to be among the top ten countries that have the highest prevalence rates of diabetes in the world, notably Type 2 diabetes (King et al., 1998). Obesity too, which was described in several members of the Ptolemys, the royal family that ruled Egypt from 305 to 30 BC (Michalopoulos et al., 2003), has now increased dramatically, particularly among Egyptian women (Galal, 2002) and is becoming a problem among Egyptian youth (Salazar-Martinez et al., 2006). Obesity and diabetes are also imposing major psychiatric challenges in Egypt (Abo Elwafa, 2002; El-Atrouni et al., 1992), and have become a subject of growing concern, at least because of the worldwide publicity regarding reported potential risk of the drug induced weight gain (e.g., Ananth et al., 2004; McIntyre et al., 2003; Ruetsch et al., 2005; Sharpe and Hills, 2003) and the diabetogenic effect of novel antipsychotics (e.g., Cohen et al., $2006_a$; Ramaswamy et al., 2006; Schwenkreis and Assion, 2004). Yet, the prevalence of the metabolic syndrome among schizophrenic patients is uncertain. Also, little is known about the relationship between serum level of a substance such as adiponectin and the metabolic syndrome among Egyptian patients with schizophrenia, at a time when in other nations the usefulness of adiponectin for the prediction of insulin resistance and metabolic syndrome is attracting much attention (Gilardini et al., 2006; Hara et al., 2006; Ogawa et al., 2005; Santaniemi et al., 2006; Tajtakova et al., 2006; Trujillo et al., 2005). The objective of this study, therefore, was to assess the prevalence of metabolic syndrome and the serum level of adiponectin in a sample of Egyptian outpatients with schizophrenia, testing the hypotheses that (a) the prevalence of the metabolic syndrome is higher among schizophrenic patients compared with a normal group of subjects, and (b) serum adiponectin level has an inverse relationship with the parameters of the metabolic syndrome in these patients.

## Method

### Participants

**Patients:** A total of 50 patients were recruited from consecutive attenders of the psychiatric out-patients clinic, Zagazig University Hospitals, Zagazig, Egypt, from July 2005 to June 2006, with a diagnosis of schizophrenia (F.20 of the ICD10) aged 18 to 60 years, for whom a stable regimen of antipsychotic medication was consistently prescribed for at least 3 months prior to recruitment. These patients had no history of chronic medical illnesses and were taking no medications, other than their antipsychotics, suspected to affect glucose or lipid metabolism. Other exclusion criteria included patients who were pregnant, active substance abusers, and those who were judged not to have the capacity to give consent.

Recruited patients were classified into two groups, the early illness group, which included patients below the age of 30 with less than 5 years' total duration of illness (N= 26), and the chronic illness group which included those above 30, with more than 10 years' duration of illness (N= 24). Patients were also classified by the type of antipsychotic as on typical (N= 15), atypical (N= 21) and mixed (N= 14).

**Controls:** 100 matched subjects who had no history of treatment for any neuropsychiatric disorder, were selected from apparently healthy hospital staff and companions of patients admitted for minor surgery, at the same hospitals, Zagazig, Egypt.

Informed consent was obtained from all participants after the procedures had been fully explained.

## Assessments

### Clinical Assessments:

Patients were subjected to a semi-structured psychiatric interview during which the ICD-10 diagnosis of schizophrenia was confirmed and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was applied. Data evaluated from all patients and controls included a standardized medical history and a thorough physical examination. Waist circumference was measured at the level of the umbilicus, at the end of a normal expiration to the nearest 0.1 cm. Blood pressure was computed as the mean of two measurements in the sitting position recorded, with an interval of 5 min of resting between measurements, from the right arm, using a mercury sphygmomanometer by auscultatory methods. During the 30 min. preceding the measurements, the subjects were asked to refrain from smoking or drinking caffeinated beverages.

### Laboratory Investigations:

All subjects were asked to abstain from food intake for at least 12 hours. Blood samples (10 ml, in two aliquots - one aliquot in EDTA and another without anti-coagulant for each participant) - were collected by venipuncture for the analysis of serum lipids [total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL) and high-density lipoprotein cholesterol (HDL)] by standard clinical biochemistry laboratory assays and for glycemia by the hexokinase method with a Dade Behring reagent on a Dimension (Dade Behring) instrument. Serum level of adiponectin by a commercial ELISA (human adiponectin ELISA kit, B-Bridge International Inc.) was also estimated according to the manufacture's instruction.

### Diagnosis of the metabolic syndrome:

The International Diabetes Federation (IDF) guidelines were used for the diagnosis of the metabolic syndrome, i.e., a central obesity, defined as waist circumference equal to or more than 94 cm and 80 cm (IDF cutoff level recommendations for Middle-Eastern men and women respectively) plus two or more of the following four factors: *1*) raised concentration of triglycerides: ≥150 mg/dl (1.7 mmol/l) or specific treatment for this lipid abnormality; *2*) reduced concentration of HDL cholesterol: <40 mg/dl (1.03 mmol/l) in men and <50 mg/dl (1.29 mmol/l) in women or specific treatment for this lipid abnormality; *3*) raised blood pressure: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or treatment of previously diagnosed hypertension; and *4*) raised fasting plasma glucose concentration ≥100 mg/dl (5.6 mmol/l) or previously diagnosed type 2 diabetes (Alberti et al., 2005).

### Statistical analysis

All data were analyzed using the Statistical Program for Social Sciences 11.0.1 software (SPSS for Windows, 2001).

**Results**

The patients group consisted of 31 men and 19 women, with a mean (± SD) age of 37.0 (±13.571) years. Table (1) compares between the demographic characteristics of patients and controls. The patients group was divided into 26 patients (17 men) with an early illness and 24 patients (14 men) with a chronic illness. The clinical characteristics of early illness and chronic illness groups of patients are given in table (2) which demonstrates that the two groups were not significantly different in their PANSS scores nor in their usage of antipsychotics. Almost all patients (48 patients; 96%) were receiving antipsychotic polytherapy, with 15 patients on typical antipsychotics alone, 19 patients on atypical antipsychotics alone and 14 patients on both typical and atypical (mixed) antipsychotics. Only one patient was on olanzapine alone and another patient was on risperidone alone. Table (3) shows no significant differences between the early illness and chronic illness groups as regard the prevalence of the metabolic syndrome or its parameters. None of the 19 patients (12 males; 7 females) and the five controls (3 males; 2 females) who met the criteria of the metabolic syndrome was previously diagnosed or treated for this condition or for any of its components. Patients, in comparison to controls, showed significantly increased values of all the parameters of the metabolic syndrome (table 4). These differences were observed whether patients were in the early illness group, or in the chronic illness group. Thus, the number of patients with metabolic syndrome, in the former group (N= 8), and in the latter group (N= 11), were significantly higher than that of the controls ($\chi^2$ =14.809; df= 1; *p* =0.000 and, $\chi^2$ =28.716; df= 1; *p* =0.000, respectively). In contrast, however, schizophrenic patients had significantly lower adiponectin level than controls (22.6 ± 8.459 vs. 30.1 ± 6.829 ng/ml; t= 5.853; df= 148; *p*=0.000). Women tended to have a higher serum adiponectin level than men. This difference reached a statistically significant level in the chronic illness group (table 5). Comparison between serum adiponectin levels, by metabolic syndrome (table 6), showed that those who got the syndrome, whether they were schizophrenic patients or controls, had significantly lower levels than those without the syndrome. In a correlation analysis, serum adiponectin level in the patients group was negatively associated with all the parameters of the metabolic syndrome except the HDL level with which it was positively associated (table 7). In the control group, however, there were no such significant correlations.

Patients, classified by the type of antipsychotic medications they were on, did not significantly differ in demographic or clinical characteristics, and as shown in table (8) they did not also differ in their serum level of adiponectin, or in the prevalence of the metabolic syndrome and its parameters.

**Table (1)** Demographic characteristics of patients and controls

| Characteristic | Patients (N= 50) | Controls (N= 100) | Analysis |
|---|---|---|---|
| Gender: Male: N (%) | 31 (62.0) | 62 (62.0) | $\chi^2 = 0.000$; df= 1; $p = 1.00$ |
| Age (years): | | | |
| Mean (± SD) | 31.6 (10.940) | 31.8 (10.808) | t= 0.112; df= 148; $p$ =0.473 |
| Education (years): | | | |
| Mean (± SD) | 11.3 (2.809) | 11.9 (2.210) | t= 1.477; df= 148; $p$ =0.142 |
| Employment: | | | |
| Employed: N (%) | 14 (28) | 39 (39) | $\chi^2$ =1.755; df= 1; $p$ =0.184 |
| Marrital satus: | | | |
| Married: N (%) | 17 (34) | 45 (45) | $\chi^2$ =1.663; df= 1; $p$ =0.197 |

**Table (2)** Clinical characteristics of patients

| | Early illness group (N= 26) | Chronic illness group (N= 24) | Analysis |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Age, years: Mean | 23.4 | 40.5 | t= 8.915; |
| (± SD) | (2.872) | (9.330) | df= 48; $p$ =0.000 |
| | | | |
| Duration of illness, | | | |
| months: Mean | 14.7 | 189.2 | t= 12.488; |
| (± SD) | (10.288) | (70.505) | df= 48; $p$ =0.000 |
| | | | |
| Age at illness onset, | | | |
| years: Mean | 20.2 | 22.0 | t= 1.606; |
| (± SD) | (2.344) | (5.188) | df= 48; $p$ =0.115 |
| | | | |
| PANSS score | | | |
| Total: Mean | 78.5 | 84.0 | t= 1.491; |
| (± SD) | (13.984) | (11.885) | df= 48; $p$ =0.142 |
| Positive: Mean | 18.6 | 19.1 | t=0.433; |
| (± SD) | (2.246) | (2.112) | df= 48; $p$ =0.667 |
| Negative: Mean | 18.3 | 19.5 | t=1.557; |
| (± SD) | (2.513) | (2.536) | df= 48; $p$ =0.126 |
| | | | |
| Antipsychotics | | | |
| Typical: N | 10 | 5 | |
| Atypical: N | 8 | 13 | $\chi^2$ =3.068; |
| Mixed: N | 8 | 6 | df= 2; $p$ =0.216 |

**Table (3)** Prevalence of metabolic syndrome and its parameters in patients

| Parameters | Early illness group N | Early illness group (%) | Chronic illness group N | Chronic illness group (%) | Analysis |
|---|---|---|---|---|---|
| | 26 | (100) | 24 | (100) | |
| Waist (M ≥ 94, F ≥ 80) | 15 | (57.7) | 17 | (70.8) | $\chi^2$ =0.935;<br>df= 1; $p$ =0.333 |
| BP (≥ 130/85) | 11 | (42.3) | 12 | (50.0) | $\chi^2$ =0.297;<br>df= 1; $p$ =0.586 |
| Glucose (≥ 100 mg/dl) | 13 | (50.0) | 11 | (45.8) | $\chi^2$ =0.087;<br>df= 1; $p$ =0.768 |
| TG (≥ 150 mg/dl) | 10 | (38.5) | 10 | (41.7) | $\chi^2$ =0.053;<br>df= 1; $p$ =0.817 |
| HDL (M<40 mg/dl, F<50 mg/dl) | 11 | (42.3) | 13 | (54.2) | $\chi^2$ =0.703;<br>df= 1; $p$ =0.402 |
| Metabolic syndrome | 8 | (30.8) | 11 | (45.8) | $\chi^2$ =1.202;<br>df= 1; $p$ =0.273 |

**Table (4)** Prevalence of metabolic syndrome and its parameters in patients compared with controls

| Parameters | Patients N | Patients (%) | Controls N | Controls (%) | Analysis |
|---|---|---|---|---|---|
| | 50 | (100) | 100 | (100) | |
| Waist (M ≥ 94, F ≥ 80) | 32 | (64) | 46 | (46) | $\chi^2$ =4.327; df= 1; $p$ =0.038 |
| BP (≥ 130/85) | 23 | (46) | 18 | (18) | $\chi^2$ =13.157; df= 1; $p$ =0.000 |
| Glucose (≥ 100 mg/dl) | 24 | (48) | 7 | (7) | $\chi^2$ =34.176; df= 1; $p$ =0.000 |
| TG (≥ 150 mg/dl) | 20 | (40) | 11 | (11) | $\chi^2$ =17.098; df= 1; $p$ =0.000 |
| HDL (M<40 mg/dl, F<50 mg/dl) | 24 | (48) | 9 | (9) | $\chi^2$ =29.545; df= 1; $p$ =0.000 |
| Metabolic syndrome | 19 | (28) | 5 | (5) | $\chi^2$ =27.009; df= 1; $p$ =0.000 |

**Table (5)** Serum adiponectin levels (ng/mL) in patients and controls, by sex

| | N | Mean | (± SD) | Analysis |
|---|---|---|---|---|
| Patients: | 50 | 22.6 | (8.459) | |
| Male | 31 | 20.8 | (7.679) | |
| Female | 19 | 25.4 | (9.088) | t= 1.923; df= 48; *p* =0.060 |
| Early illness group | 26 | 22.8 | (8.266) | |
| Male | 17 | 23.2 | (8.095) | |
| Female | 9 | 24.0 | (7.616) | t= 0.252; df= 24; *p* = 0.803 |
| Chronic illness group | 24 | 22.5 | (9.422) | |
| Male | 14 | 17.9 | (6.257) | |
| Female | 10 | 26.7 | (10.478) | t= 2.568; df= 22; *p* =0.018 |
| Controls | 100 | 30.1 | (6.829) | |
| Male | 62 | 29.8 | (6.185) | |
| Female | 38 | 30.2 | (7.487) | t= 0.320; df= 98; *p* = 0.750 |

Table (6) Mean (± SD) of serum adiponectin level (ng/mL) in patients and controls, by metabolic syndrome

| | | Metabolic Syndrome | | |
|---|---|---|---|---|
| | | Present | Not present | Analysis |
| Patients: | N | 19 | 31 | |
| | Mean | 14.7 | 27.4 | |
| | (± SD) | (±2.130) | (±7.186) | t= 7.430; df= 48; *p* = 0.000 |
| Controls: | N | 5 | 95 | |
| | Mean | 23.8 | 30.4 | |
| | (± SD) | (±10.733) | (±6.481) | t= 2.144; df= 98; *p* = 0.034 |
| Total: | N | 24 | 126 | |

| | | | |
|---|---|---|---|
| Mean | 16.6 | 29.7 | |
| (± SD) | (±6.142) | (±6.761) | t= 8.770; df= 148; $p$ = 0.000 |

Table (7) Pearson's correlation coefficients between adiponectin and the parameters of the metabolic syndrome

| Criteria | Adiponectin | | | |
|---|---|---|---|---|
| | Patients | | Controls | |
| | r | ($p$) | r | ($p$) |
| Waist | -0.295 | (0.038) | -0.174 | (0.084) |
| BP (systolic) | -0.282 | (0.047) | -0.085 | (0.400) |
| BP (diastolic) | -0.280 | (0.049) | -0.012 | (0.903) |
| Glucose | -0.388 | (0.005) | -0.073 | (0.471) |
| HDL | 0.448 | (0.001) | 0.010 | (0.925) |
| TG | -0.295 | (0.038) | -0.127 | (0.209) |

Table (8) Adiponectin and parameters of the metabolic syndrome in the patients group, by antipsychotic treatment

| | Antipsychotic Treatment | | | |
|---|---|---|---|---|
| | Typical<br>(N= 15 ) | Atypical<br>(N= 21) | Mixed<br>(N= 14) | |
| | Mean (± SD) | Mean (± SD) | Mean (± SD) | ANOVA |
| Adiponectin | 24.5 (8.895) | 19.6 (8.035) | 23.4 (8.897) | F= 1.245<br>$p$= 0.297 |
| Waist | 99.9 (13.191) | 109.2 (17.147) | 105.9 (18.821) | F= 1.245<br>$p$= 0.297 |
| BP (systolic) | 133.7 (19.682) | 136.8 (19.376) | 136.0 (19.914) | F= 0.100<br>$p$= 0.905 |
| BP (diastolic) | 87.3 (12.228) | 89.3 (11.542) | 88.2 (10.116) | F= 0.131 |

| | | | | |
|---|---|---|---|---|
| | | | | $p$= 0.877 |
| Glucose | 97.9 (24.828) | 111.7 (26.163) | 105.7 (31.796) | F= 1.149<br>$p$= 0.326 |
| HDL | 47.4 (11.219) | 42.8 (15.562) | 44.4 (14.515) | F= 0.533<br>$p$= 0.590 |
| TG | 131.1 (56.914) | 144.0 (36.797) | 138.2 (45.656) | F= 0.342<br>$p$= 0.712 |

## Discussion

To our knowledge, this is the first study from Egypt to show a high prevalence of the metabolic syndrome and its components among patients diagnosed with schizophrenia compared to normal subjects. In this study, 28% of the patients with schizophrenia fulfilled the IDF criteria for the diagnosis of metabolic syndrome, as opposed to only 3% of the matched apparently healthy comparison subjects ($p$= 0.000). Despite methodological differences, our findings are generally in line with those from other countries. Thus, in USA, for example, using baseline data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial, according to National Cholesterol Education Program (NCEP) criteria, metabolic syndrome was found to be highly prevalent (40.9%) in schizophrenia patients (McEvoy et al., 2005), and in another American study, the prevalence of the metabolic syndrome was as high as 51.2% among veterans with schizophrenia (Meyer et al., 2006). In Cuba, using the NCEP criteria, the prevalence of the metabolic syndrome was even higher (63%) in all patients with schizophrenia (41% in non-Hispanic patients and 74% in Hispanic patients) (Kato et al., 2004). In Northern Sweden, the prevalence of the metabolic syndrome among a cohort of patients with schizophrenia, according to the NCEP criteria, was 34.6% (Hagg et al., 2006). In Finland, also using the NCEP criteria, in a population-based birth cohort, 19% of the schizophrenic patients were found to have a metabolic syndrome, a 4-fold greater risk than the general population (Saari et al., 2005). Our figures, though lower than some of those found in the American and European studies, should still be considered as seriously high. Our concern is also because of the observation that there was a complete failure to detect, and hence to adequately treat, the metabolic syndrome or its components before admission to the study. Our observation, however, is in line with those of other investigators, e.g., Bo et al. (2007) who reported that more than 97% of unknown metabolic syndrome cases in their series would be identified among apparently healthy individuals when overweight/obese, and normal-BMI subjects with low physical activity were screened. Abdul-Ghani et al. (2005) found that approximately 70% of the overweight Arab population in Israel has either undiagnosed metabolic syndrome or abnormal glucose metabolism. Athyros et al. (2005) suggest that metabolic syndrome is not recognised among the general population (in Greece), and therefore, treatment and control of the syndrome and its component conditions are extremely low. Studies from various countries (e.g., Csaszar et al., 2006; Gupta et al., 2004; Tanchoco et al., 2003), including Arab countries (e.g., Al-Lawati et al., 2003; Bouguerra et al., 2006;), underscore the need for a more thorough screening in high-risk populations (Straker et al., 2005). Clearly, schizophrenic patients treated with antipsychotics ought to be considered at high risk of developing metabolic syndrome (Correll et al., 2007; Newcomer, 2004), as is confirmed by the current data. Concern about these metabolic abnormalities in schizophrenic patients is not only because of their direct, somatic effects on morbidity and mortality, but also because of their suspected association with lower adherence to medication (Weiden et al., 2004) which is equally problematic for both antipsychotic and nonpsychiatric medications (Dolder et al., 2003).

The reasons why individuals with schizophrenia are more prone to developing diabetes and metabolic syndrome than the general population remain controversial (Holt et al., 2005), but likely to be multifactorial (Fowler et al., 2005; Kahl, 2005). In the current study, the higher prevalence of metabolic syndrome and its components in patients, as compared to control subjects, was already present in the early illness group (age range: 18- 30 years), indicating a greater vulnerability to develop metabolic syndrome in patients with schizophrenia. The maintenance of having such high prevalence in the chronic illness group (age range: 31- 60 years), as compared to control subjects, suggests a long-term direct impact of the schizophrenic illness and/or negative metabolic side-effects of prolonged antipsychotic medication. This suggestion is in line with other studies (e.g., De Hert et al., 2006; Vivian, 2006). Many reports claim that second-generation antipsychotics can increase the risk of metabolic abnormalities in patients with schizophrenia (Newcomer and Haupt, 2006; Reist et al., 2007; Tarricone et al., 2006). While some researchers regarded that the situation is far from clear as regard the potential risk associated with different antipsychotic drugs (Rouillon and Sorbara, 2005), others maintained that there are obvious differential effects of second-generation antipsychotics on metabolic parameters (Haupt, 2006; Henderson et al., 2005; Lamberti et al., 2006). According to a recent US consensus statement (American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity, 2004), the second-generation antipsychotics vary in their propensity to cause obesity, hyperglycaemia and hyperlipidaemia, with clozapine and olanzapine showing the greatest effects, risperidone and quetiapine having intermediate effects, and aripiprazole and ziprasidone having lower effects. On the other hand, European (Expert group 'Schizophrenia and Diabetes 2003', 2004) and Australian (Lambert et al., 2004) consensus statements did not recognize any difference among the second-generation antipsychotics as to their propensity to cause metabolic side effects. Moreover, the American consensus statement itself acknowledges the caveat that aripiprazole and ziprasidone have fewer long-term data due to the limited amount of time they have been on the market (American Diabetes Association; American Psychiatric Association; American Association of Clinical

Endocrinologists; North American Association for the Study of Obesity, 2004). In contrast to these and other reports (e.g., Mackin et al., 2005; Wu et al., 2006) which associate metabolic syndrome more strongly with prescription of atypical antipsychotics than with prescription of typical neuroleptics, our data failed to differentiate between the typical and atypical treated groups in terms of prevalence of metabolic syndrome or its parameters. Our findings, however, may get some support from the study by Guha et al. (2005) which compared the prevalence of hyperglycaemia in Indian schizophrenic patients taking olanzapine with those taking typical antipsychotics (either haloperidol or trifluoperazine) but found no significant difference. Another study in support of our findings, reported no differential diabetogenic effect of antipsychotic treatment, irrespective of its type (typical or atypical) in a sample of European schizophrenics who were mostly on monotherapy (Cohen et al., $2006_b$). However, studies comparing patients receiving antipsychotic monotherapy, with patients on antipsychotic polytherapy, showed that the latter group had higher rates of metabolic syndrome and lipid markers of insulin (Correll et al., 2007). In the current study, comparison between the effects of antipsychotic monotherapy and polytherapy was not possible since almost all patients (96%) were on polytherapy.

Although insulin resistance is thought to be central abnormality in the pathogenesis of metabolic syndrome (Bigazzi and Bianchi, 2007; Teede et al., 2006), insulin resistance is elusive, perhaps more easily identified than measurable (Samaras et al., 2006). The WHO classification of the metabolic syndrome includes insulin resistance, but only when measured by hyperinsulinaemic euglycaemic clamp with comparison to normative background population ranges. The clamp requires bilateral cannulation, arterialisation of blood flow to the vein, 2 hours of measures, and experience. Obtaining normative sex- and ethnic-specific population data for comparison is another difficulty. Other techniques such as the frequently sampled intravenous glucose tolerance test (Pacini et al., 1986), and the insulin suppression test (Harano et al., 1977; Shen et al., 1970) are similarly complicated and cumbersome. Simpler alternative estimates have evolved, of which the homeostasis model assessment of insulin resistance (HOMA-IR) (Matthews et al., 1985) has been the most widely used, but neither it nor any of the others has become the standard for diagnosing insulin resistance (Stern et al., 2005). In the present study, the metabolic syndrome was diagnosed according to the International Diabetes Federation (IDF) criteria which do not include an assessment of insulin resistance. This omission by the IDF was not surprising because specific measurements of insulin resistance are not clinically practical (Samaras et al., 2006). We did not assess the insulin resistance in this study, but we were interested in the major adipokine secreted by fat cells, the adiponectin, irrespective of its 'complex relationship with insulin resistance' (Abbasi et al., 2004; Spranger et al., 2004). Thus, we examined the association of serum adiponectin with the parameters of the metabolic syndrome in the schizophrenic patients. Our data clearly showed that that those with the metabolic syndrome, had significantly lower levels of serum adiponectin than those without it. The difference noted between schizophrenic patients and controls could be explained by the much higher prevalence of the metabolic syndrome among these patients. Our observation that women, especially in the chronic illness group, tended to have a higher serum adiponectin level than men is supported by some studies (Arita et al., 1999; Philip et al., 2003) but not by all other studies (Ryan et al., 2003; Weyer et al., 2001). However, our observation can be explained by the fact that women tend to have less visceral fat tissue than subcutaneous fat (Wajchenberg, 2000). Recent evidence showed that serum adiponectin levels are determined predominantly by visceral and not by subcutaneous fat (Kwon et al., 2005; Steffes et al., 2006).

Many studies have shown that there may be an adiposity-hypothalamus axis designed to maintain and regulate energy balance in humans. Adiponectin is one of the important peptides associated along with this axis (Leibowitz and Wortley, 2004; Meier and Gressner, 2004; Trayhurn, 2005). Dysregulation of this axis may contribute to obesity and the development of hyperinsulinemia, which is associated with insulin resistance and diabetes (Stefan et al., 2002; Weyer et al., 2001). Development of a method for convenient prediction of metabolic syndrome in daily clinical practice presents a major challenge. From this study, we found that serum adiponectin levels were inversely associated with metabolic risk profiles in Egyptian patients with schizophrenia. This is in line with the mounting body of evidence in other populations to suggest that adiponectin is an insulin-sensitizing hormone and that the plasma level of this hormone is a predictor of the subsequent development of type 2 diabetes and metabolic syndrome (Gilardini et al., 2006; Krakoff et al., 2003).

The alterations in serum adiponectin concentration in schizophrenic patients during treatment with olanzapine or risperidone have been reported (Togo et al., 2004). However, we did not find significant differences in the serum level of adiponectin, or in the prevalence of the metabolic syndrome and its parameters between patients receiving typical, atypical or mixed antipsychotics.

In addition to the lack of an assessment of insulin resistance, certain shortcomings of our study should be mentioned. The results of our study need to be interpreted within the limitations of its cross-sectional design, moderate sample size and lack of power to examine individual antipsychotic combinations. All patients were already under treatment before inclusion into the study, and thus, we could not have a drug naïve group for comparison. In a recent preliminary study, however, Cohn et al. (2006) reported insulin resistance and susceptibility to type 2 diabetes in patients with schizophrenia who are free of antipsychotic drugs. Despite these limitations, our results should encourage clinicians who treat patients with schizophrenia to monitor for the parameters that define the metabolic syndrome as part of the ongoing management of patients treated with antipsychotics. In line with the mounting body of evidence in other populations, this study indicates that measurement of serum adiponectin level by ELISA technique may be a useful biomarker for the metabolic syndrome in schizophrenic patients.

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# متلازمة الأيض و مستوى المصل للأديبونيكتين في مرضى  الفصام المصريّين

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